

THE AMERICAN HEART JOURNAL



©Am. Ht. Assn.

ADVISORY EDITORIAL BOARD

E. P. CARTER
HENRY A. CHRISTIAN
ELLIOTT C. CUTLER
WALTER W. HAMBURGER
JAMES B. HERRICK
WILLIAM J. KERR
SIR THOMAS LEWIS
E. LIBMAN
H. M. MARVIN

JONATHAN MEAKINS
JOHN H. MUSSER
JOHN ALLEN OILLE
STEWART R. ROBERTS
G. CANBY ROBINSON
FRED M. SMITH
PAUL D. WHITE
CARL J. WIGGERS
FRANK N. WILSON

CHARLES C. WOLFERTH

PUBLISHED BI-MONTHLY
UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

Lewis A. Conner.....Editor

Associate Editors

Hugh McCulloch

Evelyn Holt

VOLUME 9
OCTOBER, DECEMBER, 1933
FEBRUARY, APRIL, JUNE, AUGUST, 1934

ST. LOUIS
THE C. V. MOSBY COMPANY

1934

COPYRIGHT, 1934, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in U. S. A.

CPA1

L 22:m73 : N25

G3

62194

Press of
The C. V. Mosby Company
St. Louis

The American Heart Journal

VOL. IX

OCTOBER, 1933

No. 1

Original Communications

INTERAURICULAR SEPTAL DEFECT ASSOCIATED WITH MITRAL STENOSIS*

SYLVESTER MCGINN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

A POST-MORTEM examination recently revealed to us an unsuspected combination of cardiac lesions that may well be recognized before death if the possibility of this diagnosis be kept in mind. A stenosed mitral valve coexisting with an interauricular septal defect was demonstrated in the heart, the roentgenogram of which appears to be distinctive. This combination of lesions like many other cardiac abnormalities has been described in the past, but it is worth while to discuss it from the viewpoint of our more modern methods of establishing clinical diagnoses and to summarize cases already reported, mostly by the French.

The increasing knowledge of individual malformations of the heart is rapidly approaching the point where the inclusive diagnosis of congenital heart disease alone is inadequate and lacks the descriptive terminology so useful in our medical nomenclature.

LITERATURE

The literature contains the reports of 23 cases in which mitral stenosis is associated with some degree of deficiency of the interauricular septum (Table I). Martineau²⁰ presented the first case in 1865 and so preceded a long series of contributions from the French investigators. The following year (1866) Peacock²² included a similar case in his book *Malformations of the Heart*. There then appeared in sequence reports of cases by Wagstaffe²⁶ (1868), Chénieux⁷ (1870), Chouppe⁸ (1872), Firket¹³ (1880), Butin⁵ (1893), Huchard and Bergouignan¹⁶ (1901), Griffith¹⁴ (1902), Tylecote²⁵ (1903), Söldner²³ (1904), Mour-eyre²¹ (1911), Dufour and Huber¹² (1911) and Heitz¹⁵ (1912). In 1916,

*From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital.

a year after Abbott's¹ case report (1915), Lutembacher¹⁰ reviewed the subject at length and discussed the various viewpoints held as to the probable etiology of the condition and the consequent alterations in the hemodynamics. As a result of his paper, the association of mitral stenosis with an interauricular septal defect has become commonly known as Lutembacher's disease. Following this, other cases have been added to the literature by Cramer and Frommel⁹ (1923), Donnelly¹⁰ (1924), Cabot⁶ (1928), Langerhon and Loheac¹⁸ (1928) and Wahl and Gard²⁷ (1931). Recently Dressler and Rösler¹¹ presented a valuable communication on the subject (1930) in which they presented a new case and described what they maintain to be typical roentgen ray findings. Theses upon the condition have been written by Bonnabel⁴ in 1906 and by Souza Gularte²⁴ in 1924.

CASE REPORT

An American letter carrier, single, fifty-six years of age, entered the Massachusetts General Hospital in June, 1932, complaining of shortness of breath, weakness, and swelling of the legs and abdomen for four years.

He had always been well except for occasional sore throats; there was no history of rheumatism, chorea, typhoid fever, or pneumonia. His father died of a lung infection, and his mother was in fair health at eighty-three years of age. Two sisters were in good health but five other siblings died in infancy.

Three years previously he had been forced to give up his position because of the same symptoms of which he complained on admission to this hospital, and at that time he had been told that he had an enlarged heart and that an x-ray picture had been suggestive of Hodgkin's disease, for which he subsequently received x-ray treatments. The physical examination in 1929 showed visible jugular pulsations, an enlarged heart with the left border in the midaxillary line, a loud systolic murmur at the mitral area transmitted to the axilla, and an arrhythmia. The abdomen was rounded and a fluid wave was obtained. Slight pitting edema was observed in both ankles. Within two months an abdominal paracentesis was done twice with the removal of amber colored fluid, following which a mass could be palpated four fingers below the costal margin. Digitalis was given and the edema partially disappeared until a return of symptoms followed an upper respiratory infection nine months ago. Since then there had been a progressive increase in his failure, and he was admitted in extremis to the Massachusetts General Hospital, where he died nine hours later.

The physical examination on entry nine hours before death showed a poorly developed man of normal height, having a grayish color, marked orthopnea, and slightly distended neck veins. The heart was enlarged to the left, and systolic and rumbling diastolic murmurs were heard at the apex without palpable thrills. The heart sounds and the pulse were of poor quality. Auricular fibrillation was present. Arteriosclerosis of the large vessels was noted and the blood pressure was recorded at 130 mm. mercury systolic and 70 diastolic. Moist râles were heard at both lung bases. There were massive edema below the waist and marked ascites. An abdominal paracentesis was done with the removal of 3100 c.c. of a slightly yellow and turbid fluid. The red count was 4,950,000, white count 7,750, and hemoglobin 90 per cent.

The x-ray film taken August 22, 1929, showed the heart shadow to be tremendously enlarged, the shadow of the right auricle being particularly prominent. There was

also a marked prominence of the pulmonary conus. The only portion of the aorta visible was the knob which was rather small. There was extensive increase in the size and density of the hilus shadows on both sides, probably due to dilated pulmonary vessels.*

The post-mortem examination was performed five hours after death. The subject was a fairly well developed but poorly nourished, middle-aged man weighing about 160 pounds. There was marked pitting edema of the lower extremities and hips with a purplish discoloration of the legs. There was a marked bluish discoloration of the face and mucous membranes.

The peritoneal cavity contained 400 c.c. of clear yellow fluid, the pericardial and left pleural cavities 100 c.c. each. The right pleural cavity was entirely obliterated by adhesions. The right lung was rather spongy but was crepitant throughout, whereas the left was crepitant except for a pyramidal area in the



Fig. 1.

Fig. 2.

Fig. 1.—Heart of present case of interauricular septal defect with mitral stenosis. R.A., right auricle; R.V., right ventricle; L.V., left ventricle; A, aorta; P.A., pulmonary artery. Note in particular the large right ventricle and pulmonary artery.

Fig. 2.—Same heart as shown in Fig. 1, with view into the left auricle from above. M.A., aperture of the stenosed mitral valve; F.O., patent foramen ovale; L.V., left ventricle.

lateral part of the upper lobe typical of an infarct. The liver weighed 1100 gm. and showed very little congestion. The cervical and inguinal nodes were negative but one axillary gland was palpable.

The heart was greatly enlarged, weighing 675 gm. On external examination a marked disproportion in the size of the right and left sides of the heart was apparent. The normal relation was reversed, the right ventricle being almost three times the size of the left. On being opened the right ventricle was found to be markedly dilated to eight or ten times the normal size and its wall was greatly thickened,

*X-ray film studied through the courtesy of the St. Elizabeth's Hospital, Boston, and interpretation kindly made for us by our colleague, Dr. George W. Holmes.

measuring 8 mm. In contrast the left ventricle was only slightly dilated and its wall was only 11 mm. in width. Both auricles were enlarged but the enlargement was greater on the right side. The right auricle measured in empty state and after fixation 11×7×6 cm. The left auricle measured roughly 9×6×4 cm. A number of scattered irregular opaque whitish milk like patches were present on the endocardial surface, chiefly of the right ventricle.

The mitral valve showed marked thickening and interadherence of the cusps producing an extreme degree of stenosis, the narrowed orifice measuring approximately 1.5 cm. in length and 3 to 5 mm. in width. There was extensive calcification of the entire ring of the mitral valve. A small (6×10 mm.) irregular nodular calcified mass projected on the undersurface of the anterior cusp and a larger calcified mass projected below and behind this downward into the ventricular muscle and extended anteriorly into the interventricular septum. The chordae tendineae were shortened and thickened.



Fig. 3.—Roentgenogram of thorax of present case of interauricular septal defect with mitral stenosis taken three years before death. Anteroposterior view. Note very large heart with marked prominence of pulmonary artery and lung hilus shadows.

All three cusps of the aortic valve showed slight diffuse thickening, most marked along the lines of closure. There was extensive fusion of the adjacent edges of the anterior and right posterior cusps with a firm, slightly nodular calcified deposit in the adherent area.

The pulmonary valve ring was markedly dilated, measuring 9.5 cm. in circumference. Except for slight thickening in the central portions of the free margin the cusps were normal.

The tricuspid valve showed slight to moderate diffuse patchy thickening most marked along the free margins. Some of the chordae tendineae were thickened and slightly shortened.

Connecting the cavities of the two auricles there was a large oval defect in the interauricular septum in the position of the foramen ovale. This measured in the

fixed specimen 2.4 cm. in the base-apex axis and 1.5 cm. transversely. The margin was sharp. The edge consisted for a width of 2 to 3 mm. of thin smooth whitish tissue of about the texture and consistency of a normal heart valve.

The coronary arteries were large with only slight atheroma. The aorta showed moderate atheroma without calcification and was 8.5 cm. in circumference in the ascending portion, 5.6 cm. in the arch, and 4.7 cm. in the descending part. The pulmonary artery was greatly dilated, measuring 10.5 cm. in circumference at a point 1 cm. above the pulmonary orifice. It was thickened with a smooth, yellowish surface and with only the slightest trace of atheroma in its smaller branches.

DISCUSSION

Pathogenesis.—An interauricular septal defect may be one of several types. The septum may be entirely lacking or represented only by a narrow remnant encircling the auricular walls. Such a condition exists when in fetal life the lower part of the auricular septum fails to develop normally. This defect is spoken of as a persistent ostium primum and when it is extreme produces a true trilobulate heart. A deficiency of the upper part of the auricular septum above the foramen ovale, which may or may not be patent, is known as a persistent ostium secundum. The foramen ovale remains patent when the primary and secondary auricular septa fail to meet or is said to be probe-patent when they meet but do not become adherent to each other, leaving an oblique passage between them. It is possible for these commonly seen probe-patent foramina ovals to become frankly patent and allow the free flow of blood through them if the septum should be greatly stretched due to distended and dilated auricles. Such were the cases reported by Martineau, Chénieux, and Butin.

In fetal life, the course of the flow of a considerable portion of blood in the heart is from the right auricle through the patency in the interauricular septum to the left auricle, and thence to the left ventricle which expels its contents into the aorta. After birth the adult type of circulation is established, and since nearly equal pressures are maintained within both auricles under normal conditions little or no admixture of blood takes place in very early life even though there may be a small opening in the septum between the auricles.

If, however, the interauricular septal defect should be complicated by some obstruction to the normal direction of blood flow as by mitral stenosis, there would be a change in the hemodynamics. The left auricular pressure would be increased over that in the right auricle with a resulting flow of blood from left auricle to right auricle. The blood is sent through the pulmonary circuit for the second time; and later, when the right auricular pressure increases sufficiently, the blood may be backed up into the venae cavae to increase the hepatic, portal and peripheral venous pressure. Under such circumstances the chambers of the right side of the heart are doing more work than are those of the left; consequently dilatation and hypertrophy of the right

auricle and ventricle and dilatation of the pulmonary artery follow, whereas the left ventricle and the aorta remain small. A similar condition exists in hearts having uncomplicated interauricular septal defects (but not to such an extreme degree as when mitral stenosis is present), which would indicate that the systolic pressure in the left auricle exceeds that in the right to some extent (the left auricle is the more uniformly muscular sac). Eventually the right ventricle may fail and the pressure within its corresponding auricle is then elevated to the point where a reversal of flow from right to left takes place. This extensive admixture of arterial and venous blood explains the occurrence of "cyanose tardive" first described by Bard and Curtillet; it is found so frequently in the terminal illnesses of patients having defects of the interauricular septum that it is almost pathognomonic of that condition. Thus is explained the absence of cyanosis in patients having this anomaly until failure of the myocardium occurs. It is reasonable to expect that extensive paradoxical embolism would take place only in the presence of some degree of cyanosis, since the flow of blood must be from the right auricle to the left; very small septal defects would permit the passage of only small emboli and would cause little or no cyanosis.

Opinions as to the relationship of the mitral stenosis and the interauricular patency have been varied. Firket¹³ in 1880 believed that the combination was due to a congenital malformation of the mitral valve and that the abnormality of the interauricular septum was a fortunate coincidence since it served as a safeguard against pulmonary congestion. Lutembacher¹⁹ considered the associations of lesions to be more than coincident or independent congenital abnormalities; he maintained that the foramen ovale was prevented from closing by the elevated left auricular pressure due in turn to the stenosed mitral valve, with resulting left to right flow of blood which was opposite to the usual intrauterine circulation. Dressler and Rösler,²¹ on the other hand, contend that an increased pressure in the left auricle would ordinarily favor the closure of the foramen ovale because of the oblique course of its canal. According to this interpretation, the congenital interauricular septal defect, small at first, but actual and not potential, would be complicated by an acquired mitral endocarditis causing stenosis of the valve, and this in time would by stretching convert a small interauricular septal patency into a larger one. We agree with these conclusions of Dressler and Rösler. Mitral stenosis would be more often complicated by open patency of the foramen ovale if these two lesions were not primarily coincidental.

Two cases of fetal endocarditis resulting in mitral stenosis at birth have been reported independently by Kockel¹⁷ and by Ayrolles.² The foramina ovals in these hearts were described as being patent to the passage of a probe, Ayrolles' case allowing water to flow from the

right to the left auricle but not in the other direction. Another case of fetal endocarditis causing mitral stenosis was reported by Donally,¹⁰ in which he states that the foramen ovale was small and guarded by a thick fold. He believes that the course of blood flow was from the left auricle to the right side of the heart and then into the systemic circulation through a patent ductus arteriosus. The pulmonary artery in this case continued as the dorsal aorta after giving off the ductus arteriosus and two pulmonary branches while the aorta remained as an example of infantile coarctation.

Clinical and Pathological Data.—The combination of mitral stenosis and interauricular septal defect is rare, only twenty-three cases having been reported in the literature; two cases, the new one reported here and the case already reported by Cabot,⁶ have been found by us in a review of 6800 autopsies at the Massachusetts General Hospital. The condition is found almost entirely in women; of the 23 cases in the literature the patient of Söldner²³ with a persistent ostium primum is the only male. Our case is the second male known to have had this condition. The lesion can be well tolerated as is indicated by the patient of Firket¹³ who died at seventy-four years of age having had eleven pregnancies, and the patient of Lutembacher¹⁰ who died at sixty-one years after seven pregnancies. Nevertheless, 11 of the 24 patients died at thirty years of age or under; the average age at death was thirty-five years, which is somewhat under that for mitral stenosis alone. The type of individual is usually below the normal average physically, being described as delicate, poorly developed, or infantile. Disorders of menstruation or tuberculosis have been noted commonly. The French believe that the general underdevelopment is due to the hypoplastic aorta and the consequent smaller blood supply. The history of rheumatic fever was definite in 3 of the 24 cases.

The physical findings are so variable that the clinical diagnosis cannot be made with confidence. Cyanosis was present in 17 of the 24 cases collected here; it appeared with the onset of failure in all except one, the case of Griffith¹⁴ whose patient became "blue in the face" upon running. Our case showed extreme post-mortem lividity but the report of the physical examination noted only a peculiar grayish color before death. Some authors have emphasized the point that cyanosis may be absent terminally. Clubbing was seen in only one case.

An apical systolic murmur was heard in 15 cases and was the most common auscultatory finding. It was accompanied by a diastolic murmur maximal at the apex in eight cases, and by an apical thrill in four, of which two were continuous, one systolic, and the timing of the other was not noted. Mitral diastolic murmurs were heard alone in four individuals, and in three of these there were palpable presystolic thrills. Systolic murmurs were heard at the base of the heart in four

TABLE
INTERAURICULAR SEPTAL DEFECTS

NAME OF AUTHOR	DATE OF REPORT	SEX	AGE AT DEATH	CYANOSIS	MURMURS				THRILL	SIZE OF PULSE	HEART WEIGHT	SIZE OF MITRAL VALVE	OTHER VALVE INVOLVE- MENT		
					SYSTOLIC		DIASTOLIC						AORTIC	TRICUSPID	PULMONARY
					APEX	BASE	APEX	BASE							
PATENT FORAMEN OVALE															
Martineau	1865	F	28	+	+	+	+	+	+					+	
Peacock	1866	F	16	+							230	3.1 cm.			
Chénieux	1870	F	27		+						720				
Chouppe	1872	F	48		+	+				Small	470	Tips of two fingers	+	+	
Firket	1880	F	74	+	+					Small			+	+	
Butin	1893	F	32	+	+					Small	480	Finger tip	+		
Tylecote	1903	F	43	+	+		+				660	Two finger tips			
Dufour and Hubert	1911	F	26				+		+	Small		Fibrous stenosis			
Heitz	1912	F	43	+						Small	440	Finger tip		+	+
														In.	
Abbott	1915	F	38	+			+		+			Button hole			
Lutembacher	1916	F	61	+	+		+			Small		Rigid cone			
Cramer and Frommel	1923	F	41		+		+		+					+	
Donnally	1924	F	57 hr.	+		+						Funnel shaped			
Langerhon and Loheac	1928	F	54	+	+		+				540	Half-moon		+	
														In.	
Dressler and Rösler	1930	F	30	+	+					Small		Fusion of leaflets			
Wahl and Gard	1931	F	21	+			+		+		623	4.5 cm.			
cGinn and White	1933	M	56		+		+			Small	675	Marked stenosis	+	+	+

I

WITH MITRAL STENOSIS

DILATED				HYPERTROPHIED				SIZE OF PULMONARY ARTERY	SIZE OF AORTA	SIZE OF INTER-AURICULAR OPENING	REMARKS ABOUT THE INTERAURICULAR OPENING
RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE THICKNESS OF WALL	LEFT VENTRICLE THICKNESS OF WALL				
				+	+			Normal	Small	Not stated	Patency due to distended auricles. Clot found in foramen ovale.
+	+	+				+				Admits a shilling	Entirely unclosed.
+	+	+	+							Admits a finger tip	Patency due to dilatation of the auricles.
+		+					2 cm.		Small	Admits a thumb	Widely open foramen ovale.
+	+	+	+							1x2.5 cm.	Foramen ovale open.
+		+	Small				Small	Large	Small	1 cm. x 7 mm.	Closed by thin membrane except for opening in anterior part; opening due to dilated auricles.
+	+			+	+					2 inches diam.	Round foramen ovale.
										4 cm. diam.	Patent foramen ovale.
+	+						Small			Slit opening	Foramen ovale open due to dilated auricles. Holes in posterior membrane allow direct communication.
+	+	+		+	+	+		9 cm. circum.	7 cm. circum.	2x1.5 cm.	Gaping foramen ovale incapable of closure.
+	+	+	Small	+		+	Small	Large	Small	3x4.5 cm.	Foramen ovale open.
+		+		+		11 mm.	11 mm.	9 cm. circum.	3.6 cm. circum.	3x5x2 cm.	Foramen ovale open.
+		+			Small		Small			Small	Foramen guarded by a fold but freely open into the right auricle. Ductus arteriosus patent. Infantile coarctation of aorta.
+	+	+	Small	+	+	+	Small			Admits a franc piece	Foramen ovale open.
+		+		+		+	Small	10 cm. circum.	4 cm. circum.	3x4 cm.	Foramen ovale open.
						20 to 35 mm.	10 to 15 mm.	4.3 cm. diameter	1.6 cm. diameter	22 mm. diameter	Foramen ovale wide open.
+	+	+		+	+	8 mm.	11 mm.	10.5 cm. circum.	8.5 cm. circum.	2.4x1.5 cm.	Patent foramen ovale with sharp edges.

TABLE

NAME OF AUTHOR	DATE OF REPORT	SEX	AGE AT DEATH	CYANOSIS	MURMURS				THURILL	SIZE OF PULSE	HEART WEIGHT	SIZE OF MITRAL VALVE	OTHER VALVE INVOLVEMENT		
					SYSTOLIC		DIASTOLIC						AORTIC	TRICUSPID	PULMONARY
					APEX	BASE	APEX	BASE							
INTERAURICULAR SEPTAL DEFECT—PERSISTENT OSTIUM PRIMUM.															
Huchard and Bergouignan	1901	F	34	+		+	+	+				Finger tip	+	+	+
Griffith	1902	F	13	+	+		+		+		700	Stenosis			
Tylecote	1903	F	39	+			+			Weak	1100	Fibrous stenosis			
Söldner	1904	M	30		+							Aortic leaf thick			
INTERAURICULAR SEPTAL DEFECT—PERSISTENT OSTIUM SECUNDUM															
Wagstaffe	1865	F	52									Finger tip	+	+	
													St.	In.	
PATENT FORAMEN OVALE AND AN ADDITIONAL INTERAURICULAR SEPTAL DEFECT															
Moureyre	1911	F	29	+	+					Small	550	Rigid ring		+	
														In.	
Cabot	1926	F	24	+	+		+		+	Poor	665	7 cm. cir- cum. de formed	+	+	+

cases, accompanied by early blowing diastolic murmurs in two. The pulse was never described as being of good quality; it was frequently found to be irregular. Two cases had electrocardiograms which showed right axis deviation.

The post-mortem examinations have shown large hearts with weights far above normal. Tylecote's²⁵ patient had a heart weighing 1100 gm. but this included the adherent pericardium. The cardiac enlargement has been found to be due primarily to dilatation and hypertrophy of the right auricle and ventricle. The left auricle frequently shows similar changes, but the left ventricle is usually of small size. Dilatation of the pulmonary artery in the presence of a small aorta is common, this relationship having been observed in 13 cases. The extent of the mitral stenosis and the degree of the interauricular patency have varied considerably as is indicated in Table I.

I—CONT'D

DILATED				HYPERTROPHIED				SIZE OF PULMONARY ARTERY	SIZE OF AORTA	SIZE OF INTER-AURICULAR OPENING	REMARKS ABOUT THE INTERAURICULAR OPENING
RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE THICKNESS OF WALL	LEFT VENTRICLE THICKNESS OF WALL				
+	+	+		+	+	+	+		Small	4x5 cm.	Septum consists only of a fine ridge around auricular wall.
+	+	+	+					2¼ in. circum.	1½ in. circum.	1½x2½ in. circum.	Septum absent except for a remnant of fenestrated membrane.
+		+		+		+		Large	Small	2 inches	Septum absent except for a remnant on the anterior wall.
+		+		+	7 mm.	17 mm.	17 mm.	6.7 cm. circum.	5.2 cm. circum.	1.5 cm. diam.	Membrane across foramen ovale. Hole surrounded by a membrane just above aortic cusp of the mitral valve.
	+		+		+		+			Large	Large aperture 1 inch below the superior vena cava. Foramen ovale closed.
+	+	+				+			Small	Large and small	Small perforation in anterior membrane.
+		+				6 mm.	9 mm.	Large	Small	1 cm. diam. and finger tip	Hole admitting finger tip in septum above patent foramen ovale.

Roentgenography.—The consistent pathological findings might be expected to give correspondingly consistent roentgenograms. Cramer and Frommel⁹ described the heart as being a "coeur en sabot" with a prominent pulmonary arc. Lutembacher commented upon the enlargement of the right chambers, which he believed caused the apex to be blunt and raised above the diaphragm whereas in pure mitral stenosis the left border of the heart is more vertical. The report in Cabot's⁶ case is quoted as follows: "The x-ray showed a mass which did not pulsate at the right of the heart. The pulsations of the heart itself were very indistinct. The outline of the heart shadow with the poor pulsation suggested pericardial disease. There was extensive mottling extending out from both lung roots."

Dressler and Rösler¹¹ have noted the presence of a narrow aorta with a consequent diminution of the shadow of the aortic knob in ad-

dition to the other findings. They consider the appearance of the heart to be that either of pure mitral stenosis or of an interauricular septal defect alone but with an exaggeration of all the findings due to the combined effect of the two lesions. They insist that all the features mentioned above are essential to the diagnosis; these features include the large pulmonary conus, the narrow aorta, the extensive right-sided hypertrophy, and the wide lung hilus shadows. The roentgenogram of our case conforms to their criteria and agrees in detail with the orthodiagram included in the thesis of Souza Gularte. The report of Wahl and Gard²⁷ is accompanied by reproductions of the roentgenograms in their case. The consistency of this x-ray evidence is convincing. It is of interest to observe that so dense are the mediastinal shadows that two cases were actually given x-ray radiation for tumors of the mediastinum and one of them subsequently underwent an operation in an attempted surgical removal of the suspected growth, which proved to be the dilated pulmonary artery.

SUMMARY

1. The clinical and pathological findings in 24 cases showing the combination of mitral stenosis and interauricular septal defect have been summarized herewith; these include the 23 cases previously reported in the literature and a new case of our own (a man fifty-six years old).

2. The abnormal alterations in the blood flow through the heart have been described.

3. The diagnosis of this combination of lesions may be made from the fairly typical roentgenogram and suggestive clinical signs. The roentgenogram corresponds with the post-mortem findings showing a large rounded heart especially prominent to the right, an exaggerated pulmonary conus, wide lung hilus markings, and a narrow aorta.

REFERENCES

1. Abbott, M. E.: Two Cases of Widely Patent Foramen Ovale, *Bull. Internat. Assoc. Med. Museums* 5: 129, 1915.
2. Ayrolles, P.: Malformations congénitales des viscères et des membres, *Rev. mens. des maladies de l'enfance* 3: 222, 1885.
3. Bard and Curtillet: Contribution à l'étude de la physiologie pathologique de la maladie bleue. Forme tardive de cette affection, *Rev. de méd.* p. 993, 1889.
4. Bonnabel, J.: Contribution à l'étude de quelques affections congénitales du cœur, *Paris Thesis*, 1906.
5. Butin: Étude sur la communication accidentelle des deux oreillettes du cœur, *Paris Thesis* 4: 412, 1892-3.
6. Cabot, R. C.: *Facts on the Heart*, Philadelphia, 1926, p. 754, W. B. Saunders Co.
7. Chénieux: Hypertrophie du cœur avec dilatation de toutes les cavités et agrandissement du trou de Botal, *Bull. Soc. Anat. de Paris*, 1870.
8. Chouppe: Insuffisance et rétrécissement de l'orifice mitral; rétrécissement sous-aortique. Persistance du trou de Botal, *Bull. Soc. Anat. de Paris* 47: 295, 1872.

9. Cramer, A., and Frommel, E.: Contribution a l'étude du rétrécissement mitral congénital associé à l'insuffisance interauriculaire, *Arch. des mal. du coeur* 16: 561, 1923.
10. Donnally, H. H.: Congenital Mitral Stenosis: Report of a Case of Developmental Mitral Stenosis Combined With Hypoplasia of the Left Ventricle and Auricle, Rudimentary Aorta, and Other Developmental Defects, *J. A. M. A.* 82: 1318, 1924.
11. Dressler, W., and Rösler, H.: Vorhofseptumdefekt kombiniert mit Mitralstenose und Aurikulärem Leberpuls, *Ztschr. f. klin. Med.* 112: 412, 1930.
12. Dufour, H., and Huber, M.: Presentation d'un coeur montrant une persistance du trou de Botal de dimensions considérables ayant évolué sans cyanose, *Bull. et mem. Soc. méd. des Hôp. de Paris*, p. 510, 1911.
13. Firket, C.: Examen anatomique d'un cas de persistance du trou ovale de Botal, avec lésions valvulaires considérables du coeur gauche, chez une femme de 74 ans, *Ann. Soc. méd.-chir. de Liège*, p. 188, 1880.
14. Griffith, O. W.: A Case of Almost Complete Absence of the Auricular Septum and Other Cardiac Malformations Complicated by Acquired Mitral Disease, *Manchester M. Chr.* 4: 385, 1902.
15. Heitz, J.: Un cas de rétrécissement mitral avec persistance du trou de Botal, *Bull. Soc. Sc. Méd. de Clermont-Ferrand*, 1912.
16. Huchard and Bergouignan: Communication interauriculaire, rétrécissement mitral, et aplasie artérielle d'origine congénitale, *Bull. et mém. Soc. méd. des Hôp. de Paris* 18: 757, 1901.
17. Kockel, R.: Beitrag zur Kenntniss der angeborenen Endocarditis, *Verhandl. d. Gesellsch. deutsch. Naturf. u. Aertzt.*, Leipzig 80: 39, 1908.
18. Langerhon, L., and Loheac, P.: Sur un cas de rétrécissement mitral avec persistance du trou de Botal, *Paris méd.* 51: 545, 1928.
19. Lutembacher, R.: De la sténose mitrale avec communication interauriculaire, *Arch. des mal. du coeur* 9: 237, 1916. La sténose mitrale avec communication interauriculaire, *Presse méd.* 33: 236, 1925.
20. Martineau: Sur un cas de rétrécissement mitral avec persistance du trou de Botal, *Bull. Soc. des sc. méd. Clermont-Ferrand*, March, 1911.
21. Moureyre: Un cas de rétrécissement mitral pur avec persistance du trou de Botal, *Bull. Soc. d. sc. méd. Clermont-Ferrand*, 1911.
22. Peacock, T. B.: *Malformations of the Heart*, London, 1866, p. 116, ed. 2, John Churchill and Sons.
23. Söldner, F.: *Missbildungen der Vorhofscheidewand des Herzens (ostium primum persistens)*, Munich Thesis, 1904.
24. Souza Gualarte, J. G.: La sténose mitrale avec communication interauriculaire, *Paris Thesis*, 1924.
25. Tylecote, F. E.: Defects in the Auricular Septum, *Lancet*, p. 821, 1903.
26. Wagstaffe, W. W.: Case of Free Communication Between Auricles by Deficiency of the Upper Part of the Septum Auriculorum, *Tr. Path. Soc. London* 19: 96, 1868.
27. Wahl, H. R., and Gard, R. L.: Aneurism of the Pulmonary Artery, *Surg. Gynec. and Obst.* 52: 1129, 1931.

PAROXYSMAL PULMONARY HEMORRHAGES*†

THE SYNDROME IN YOUNG ADULTS WITH MITRAL STENOSIS

B. S. OPPENHEIMER, M.D., AND SIDNEY P. SCHWARTZ, M.D.
NEW YORK, N. Y.

SEVERE paroxysmal pulmonary hemorrhages, not due to intrinsic disease of the lungs, are very infrequent in patients with chronic rheumatic valvular heart disease and mitral stenosis. Only 3 of the last 1000 patients with mitral stenosis admitted to the Montefiore Hospital gave a history of such recurrent pulmonary hemorrhages. Of these, 2 were females and 1 was a male.

The syndrome is characterized by the sudden onset of cough with profuse bright red expectoration in an afebrile and usually ambulatory patient with mitral stenosis in whom, as a rule, there is little evidence of congestive heart failure. The respirations and pulse are increased, the breathing may be of the asthmatic type, there is profuse sweating, and the bleeding may be very abundant although inconstant. It may come in spurts and last as long as four days at one time. It may recur periodically each month and in young girls it has been mistaken for vicarious menstruation.

While the symptom complex has been variable in each particular case, the clinical picture of all, as observed over a prolonged period of time, has been so strikingly uniform that it has been thought worth while to describe some of these cases in detail. The prognosis as to life of these younger patients with paroxysmal hemorrhages associated with mitral stenosis, once the symptom complex has appeared, is very grave.

REPORT OF CASES

CASE 1.—History No. 1249-R. Diagnosis: C.R.C.V.D., mitral stenosis and insufficiency, and paroxysmal pulmonary hemorrhages.

F. S., a young woman, aged twenty-two years, was admitted to the Montefiore Hospital on November 21, 1924, and died on April 29, 1930.

Previous History.—At the age of thirteen she had a bout of chorea with the movements limited to the right side of the body. She was advised at that time to have her tonsils removed but tonsillectomy did not abolish her choreiform movements, although they were much milder for the next three years. In September, 1923, when she was sixteen, she entered a hospital because of severe palpitation of the heart and after remaining there for eight weeks, she was sent to a convalescent home. One year later she entered the Montefiore Hospital because of extreme restlessness, irritability, and palpitation of the heart.

Physical Examination.—On admission the patient appeared to be tall and poorly-nourished for her age. She showed marked twitchings of her fingers and of her right arm. The neck veins were not distended. There was a bulging of the left

*From the Medical Division of the Montefiore Hospital.

†Read before the American Heart Association, Milwaukee, Wisconsin, June 13, 1933.

half of the chest in the region of the third, fourth, and fifth costosternal junctions. The apical impulse of the heart was in the fifth intercostal space to the left of the midclavicular line. The first heart sound was accentuated and was preceded by a rough rumbling diastolic murmur. P_2 was loud. The heart rate averaged 118 beats per minute, and there was marked sinus arrhythmia. The blood pressure was 120/90. The lungs were clear. The liver and spleen were not palpable, and there was no edema of the lower extremities.

The laboratory findings, including the blood Wassermann reaction, were negative.

Radiographic examination of the chest failed to show any abnormalities of the lungs. The left ventricle was slightly rounded, and there was a bulging of the pulmonary artery. The left auricle encroached upon the retrocardiac space. The electrocardiogram showed right axis deviation, with T_2 and T_3 negative. (The patient was not receiving any digitalis.)

Course and Progress.—During her first few weeks in the hospital she remained in bed most of the time because of the marked increase in her pulse which always averaged over 100 beats per minute. However, since she was afebrile and her heart rate was noted to be under 60 when she was sound asleep, the girl was discharged on August 9, 1925, and advised to report to the clinic. She remained well and was up and about until April 14, 1927, when she was readmitted with a severe pain in the right groin and a sharp, lancinating pain in the right scapular region.

On this day she had taken a short walk when she became suddenly aware of being unable to catch her breath. She hailed a taxicab and while riding home, her breathing became very labored and she began to expectorate large amounts of blood-tinged sputum. She was rational and not alarmed. Throughout her trip home she was forced to cough because of severe irritation in the throat. The labored breathing and expectoration stopped with rest in bed, but on the morning of April 18, 1927, while she was in the hospital, she experienced a very severe hemorrhage from the lungs.

When seen at this time, her face was ghastly white. There were large beads of perspiration on her forehead. Respirations were rapid, averaging 34 per minute, and there was a profuse bright red, bloody discharge coming out from her mouth and through her nostrils. Frequently, at irregular intervals, there would be a sudden rasping cough, accompanied by large gushes of bloody fluid. The pulse was rapid and thready and averaged 170 beats per minute, but the rhythm was regular. The heart sounds were inaudible. The lung fields revealed large, moist, bubbling râles. The liver did not enlarge.

This seizure of blood spitting lasted about half an hour, after which she sat up in a chair and felt easier. On the same evening, however, she had another hemorrhage which lasted forty-five minutes after the administration of large doses of morphine sulphate. On the following morning her breathing was asthmatic in type. Expiration was prolonged and inspiration was difficult. There was still some cough with bright red expectoration but not so severe as on the previous day. Such mild bloody expectoration continued for the next five days. During all this time she was kept warm with blankets and given fluid parenterally, since she vomited almost everything she took by mouth.

On the morning of May 1, 1927, she began to complain again of pains in the groins with right scapular tenderness, and within one hour she suffered another very severe hemorrhage. This was as abundant as one of the large and profuse hemorrhages that are seen in patients with tuberculosis. A series of drugs were tried to prevent any further bleeding, but they were all of no avail. She ceased to spit any blood-tinged sputum five days later.

During this episode a radiographic examination of her chest was reported as revealing "partial consolidation" of both lower lobes with more extensive involve-

onset, coughing set in, and shortly the breathing became asthmatic in type. Within ten minutes there was frothy expectoration with blood-tinged sputum. Shortly this became profuse and bright red in color, and was brought up in large quantities with each coughing spell. It became so profuse that it poured out of the nostrils. The coughing would stop for a while and then increase spasmodically when the bleeding would recur. At this time the material expectorated looked like pure blood. The frothiness had disappeared and yet there were no clots in the blood. This continued in recurrent spurts for half an hour before it ceased, leaving the girl in an exhausted condition. The asthmatic type of breathing continued for the rest of that day.

Between this day and July 13, 1930, when she died, following an unusually prolonged attack, she had ten other similar episodes, some, however, not so severe. Sometimes associated with the onset of one of these attacks, she presented evidences of somatic hallucination and delusions. She was apparently well oriented but had a tendency to fabricate. She was unquestionably psychotic, but it was difficult to state whether the psychosis was due to the onset of the acute episode or part of her cardiac disease.

Death followed a prolonged seizure of mild blood spitting which was preceded by a mental derangement that necessitated physical restraint.

Autopsy (No. 5002) performed thirty-two hours post mortem by Dr. J. J. Vorzimer. (Only the interesting findings are reported):

The heart weighed 200 grams. The pericardium was smooth and glistening and showed no abnormalities. There were a few areas of hemorrhage in the epicardium over the auricles. The epicardial fat was moderate in amount and sharply defined from the muscle. The myocardium was firm and slightly thickened. The aortic, pulmonary, and tricuspid valves showed no abnormalities. The mitral valve was of the "button-hole type" and showed fusion and thickening of the two leaflets. There were a few small, white thickenings on the auricular surface of the aortic leaflet near its edge. The papillary muscles were hypertrophied and the chordae tendineae were shortened. The coronary vessels showed no abnormalities and were patent throughout. The left auricle was somewhat dilated and hypertrophied, and there was some hypertrophy of the right ventricular wall.

The pleura was smooth and glistening over both lungs except for a few scattered areas of fine fibrin on the upper lobe. Both lungs were crepitant, except in the upper lobes which felt fleshy and firm. On section both upper lobes presented dry, dark red, homogeneous surfaces from which blood and a small amount of serum could be expressed.

The lower lobes on section showed slight edema and had pink surfaces mottled with areas of anthracosis. From these surfaces a frothy, pinkish colored serum could be expressed. The bronchi showed no abnormalities. The pulmonary vessels showed many raised yellowish plaques.

Microscopic examination of some of the lung tissue showed the pleura to be thick and congested. The alveoli were filled with red cells, desquamated epithelial cells, serum, and "heart failure" cells. The vessels showed thickening of the intima. The alveolar capillaries were tremendously congested.

Other alveoli were emphysematous and the walls of the bronchioles showed well-defined areas of lymphocytic infiltration. There was marked increase of the perivascular fibrous tissue. Several of the bronchi showed marked engorgement of the capillaries in the mucosa.

CASE 3.—History No. 20828-R. Diagnosis: C.R.C.V.D., mitral stenosis and insufficiency, paroxysmal pulmonary hemorrhages.

M. G., male, aged nineteen years, was first admitted to the Montefiore Hospital on February 2, 1932, and has been under our observation ever since. His chief

When the physician is called to the bedside of a patient who is suffering from a disease of the heart, he is often confronted with a situation which is not only a medical but also a social problem. The patient may be a member of a family which is financially unable to pay for the best medical care, or he may be a member of a family which is so situated that the patient is unable to leave his home. In such cases the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself. In the following pages, we shall discuss some of the factors which enter into the decision, and we shall try to show how the physician can best handle the situation.

The first factor which enters into the decision is the nature of the disease. If the disease is one which is likely to be fatal, and if the patient is in a condition which is such that he is unable to take care of himself, the physician is often faced with the question of whether or not he should treat the patient at all. In such cases, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The second factor which enters into the decision is the financial situation of the patient. If the patient is a member of a family which is financially unable to pay for the best medical care, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The third factor which enters into the decision is the social situation of the patient. If the patient is a member of a family which is so situated that the patient is unable to leave his home, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The fourth factor which enters into the decision is the physician's own feelings. If the physician feels that he is unable to treat the patient, or if he feels that he is unable to treat the patient under the conditions which are presented, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The fifth factor which enters into the decision is the physician's own conscience. If the physician feels that he is unable to treat the patient, or if he feels that he is unable to treat the patient under the conditions which are presented, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The sixth factor which enters into the decision is the physician's own sense of duty. If the physician feels that he is unable to treat the patient, or if he feels that he is unable to treat the patient under the conditions which are presented, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The seventh factor which enters into the decision is the physician's own sense of responsibility. If the physician feels that he is unable to treat the patient, or if he feels that he is unable to treat the patient under the conditions which are presented, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

The eighth factor which enters into the decision is the physician's own sense of honor. If the physician feels that he is unable to treat the patient, or if he feels that he is unable to treat the patient under the conditions which are presented, the physician is often faced with the question of whether or not he should treat the patient at all, and if so, under what conditions. The answer to this question is often a difficult one, and it is one which the physician must answer for himself.

complaints on admission were repeated blood-spitting episodes, and almost constant pain in the back between the shoulder blades, and palpitation of the heart.

Previous History.—Four years prior to his admission he was advised by school physicians that he had chronic valvular heart disease. Two years later he was suddenly awakened one night with a severe coughing spell, difficulty in breathing, and palpitation of the heart. He claims that shortly after the onset of this seizure he brought up large quantities of "pure blood." With the subsidence of this episode,



Fig. 1.—(Case 3) A roentgenogram of the chest obtained during the interval when the patient was free from symptoms. The heart shadow shows moderate rounding of the left ventricle and the lung fields are clear, with the exception of the hilar shadows which are accentuated.



Fig. 2.—(Case 3) A roentgenogram of the chest obtained two days after the onset of a paroxysmal seizure of pulmonary hemorrhage. Note that the hilar shadows are markedly accentuated and that there is diffuse transudation within the entire right upper lobe and almost the whole of the left lung with the exception of its apex.

he developed sticking pains in the back between his shoulder blades in the region of the first four dorsal vertebrae. Incidentally, he complained of drawing pains in his legs and muscles, so that he could hardly move. Several hours later he was transferred to the Bellevue Hospital where he remained for six days, although the blood spitting disappeared twelve hours after the onset of the attack.

Eight weeks before admission to the hospital he experienced a similar episode of paroxysmal bleeding from the lungs which, however, was not severe and lasted only

one hour. Since then he has been ambulatory but has been having recurrent seizures of palpitation of the heart and occasional missed beats.

Physical Examination.—The boy appeared well-nourished. There was no evidence of any dyspnea, and his neck veins were not distended. The apical impulse of the heart was in the fifth intercostal space to the left of the midclavicular line. The first heart sound was accentuated and was partly obscured by a soft blowing systolic murmur which in turn was followed by a short rough rumbling diastolic murmur. The heart rate averaged 86 beats per minute and the rhythm was regular. The systolic blood pressure was 126 mm. of mercury and the diastolic 92 mm. of mercury. The lungs were free from moisture. The liver and spleen were not palpable, and there was no edema of the lower extremities.

Radiographic examination of the chest showed some pleural thickening in the right costophrenic angle. There was moderate haziness of the pulmonary fields. The heart was placed vertically. The pulmonic artery and conus portion of the right ventricle showed some enlargement. The left ventricle was not definitely enlarged. The electrocardiogram showed right axis deviation.



Fig. 3.—(Case 3) A roentgenogram of the chest obtained four days after the onset of a paroxysmal seizure of pulmonary hemorrhage. Note that both the bases and apices are now clear, while the root shadows are still markedly accentuated.

Course and Progress.—At 10:30 P.M., February 29, 1932, the boy began to complain of severe pain in the lower region of his spine. When seen then he appeared very apprehensive and was tossing from side to side. Soon his head was thrown backward and he assumed a position of opisthotonus. His legs, however, were extended forcibly, and he resisted any attempts at flexing them. He complained of great pains when he was touched or moved. It was necessary to restrain him because of his violence.

His face had an anxious expression and his entire body was covered with large beads of perspiration. His pupils were dilated but they reacted to light and in accommodation. His speech was incoherent and he complained that his teeth were "falling" out. By distracting his attention it was found possible to press hard over his dorsal region without eliciting any tenderness.

At midnight of this day his pulse was 80 and his respirations were normal. The lungs did not reveal any moisture, but on the following morning he was awakened after a coughing spell and then vomited a large quantity of coffee-ground material. Shortly he began to expectorate frothy, tinged sputum, and thereafter he frequently brought up quantities of bloody fluid for the next three days. At this time there

were diffuse râles over both of his chests, anteriorly and posteriorly, from the apex to the base. His temperature was elevated to 101° F., and he showed moderate increase in the leucocyte count.

An x-ray examination of the dorsal spine obtained on March 1, 1932, during this episode did not reveal any changes in the bones of his spine. Roentgen examination of the chest on this day showed dense shadows on both sides, extending from the hilum well outward toward the axillary region. The apical regions of the lungs, as well as the extreme bases on both sides, appeared clear. Three days later, when his blood spitting had ceased, the lungs were clear again and most of the shadows just described had disappeared.

In the next six months he was seen and studied during several of these attacks, each one of which was associated with an "aura" consisting of psychogenic manifestations. Apparently the boy had premonition of the onset of these attacks. He became apprehensive for several hours before their appearance. Palpitation of the heart was the first sign. His heart rate would rise from an average of 90 beats per minute to 140 beats, but the electrocardiograms invariably revealed normal sinus rhythm. The pain in the back, of which he always complained, would be augmented at these times, and the opisthotonus position which he assumed appeared to be one in which he was most comfortable at such times. Difficulty in breathing accompanied by profuse perspiration appeared after that, and then recurrent coughing spells would indicate the approach of the blood-spitting episode. At times he would talk irrationally for hours before the appearance of the lung signs, and often he would sleep through these attacks, when the vomiting of dark-ground material would point to the fact that he had had a seizure through the night and had swallowed most of the fluid. More often, frank bloody fluid would flow from both his mouth and nostrils. Peculiarly enough, the psychic disturbances would all pass away with the onset of the bloody expectoration. In between attacks he would be perfectly comfortable and at present is up and about most of the time, having been free from symptoms for about two months.

DISCUSSION

Blood spitting in one form or another has been well known to the older clinicians as a common manifestation of patients with heart disease. The French called it "hemoptosie cardiaque" or "forme hemoptoique des maladies du coeur."^{1, 2} But in most instances it was only the occasional red-streaked sputum that focused the physician's attention to the underlying cardiac lesion. And in the era prior to the x-rays, it was common practice, in the absence of any definite physical signs, to eliminate a tuberculous process as the cause of the mischief by the presence of "heart failure cells" in the rusty sputum of such patients.³ We now know that other causes of such blood spitting in patients with heart disease may be due to intrinsic disease of the lung independent of the heart lesion, such as cancer of the lung, bronchiectasis, and varices of the bronchi, to mention only a few of the conditions which we have encountered in our experience with such patients.

Severe hemorrhages, however, in the presence of mitral stenosis have been rather uncommon even with massive infarction of the lung,^{4, 5, 6, 7} and for this reason the various manifestations which these patients exhibit place them in a different category from others with heart disease.

THE CLINICAL SYNDROME

The attacks for which these patients seek relief are characterized by periodically recurring seizures of blood spitting heralded at times by an aura with psychogenic manifestations; severe palpitation of the heart with a marked increase in the pulse rate; pains in the back between the shoulder blades extending down the spinal region, and difficulty in breathing accompanied by paroxysmal coughing ending at times in severe pulmonary hemorrhages.

These attacks usually appear in ambulatory young adults with mitral stenosis many years after the initial bout of rheumatic fever and may be the first evidence of the presence of heart disease. Signs of congestive heart failure are usually absent. The seizures vary in number from one to several a month, and their increase in frequency and duration is always of ominous prognostic significance. They have never been noted during an active bout of rheumatic fever, and in only one instance were they preceded and accompanied by a slight rise in temperature lasting two days.

The Psychogenic Manifestations.—Sometimes they are preceded by an aura lasting several hours before the actual attack is ushered in. There is mental anguish with a fear of something grave impending. The sensorium becomes cloudy and the speech is frequently unintelligible. Hallucinations appear, there are visual disturbances, and the patient may go through all sorts of contortions and body movements that are uncoordinated. In the absence of objective localizing neurological signs, some have been suspected of malingering, and one girl who was admitted to the neurological service of an institution was considered to be suffering from major hysteria. She died shortly after, following a severe hemoptysis and autopsy revealed a tight mitral stenosis, without any infarcts in the lung or points of bleeding from any of the pulmonary vessels. In two girls, the slight mental disturbances appearing prior to such seizures were thought to have been due to the associated menstrual changes, and in these instances the blood spitting was considered as vicarious menstruation, no consideration being given to the underlying mitral disease present. The neck rigidity and opisthotonus in one boy, a position assumed by him prior to the onset of the attacks, presumably because of the accompanying severe pain in the back, led to the diagnosis of meningitis, and he was subjected to spinal taps, with no abnormal findings, of course.

The mental disturbances become graver with the increase in the frequency and duration of these episodes, and in some patients the manic-depressive symptoms have compelled us to use physical restraint.

Skin Manifestations.—In one boy a severe generalized urticarial eruption appeared on four separate occasions several hours prior to the development of his paroxysms of coughing, and there was alternate blanch-

ing and cyanosis of several of the fingers before profuse perspiration covered the entire body. The skin eruptions disappeared within five hours.

Pains in the Back.—Sometimes the first evidence of an oncoming seizure may be a sharp pain in the back between the shoulder blades. It may be well localized for several hours, but then may radiate along the region of the spinal column as far down as the lumbar vertebrae. This pain is, as a rule, unassociated with tenderness. Only rarely have the pains been localized to any other region. In one girl they were severest in both groins in addition to the interseapular region.

Palpitation of the Heart.—Associated with these pains there is invariably palpitation of the heart. The heart rate may increase up to 150 or 170 beats per minute, and with this acceleration there is violent pulsation of the vessels of the neck. The rapid beating of the heart may persist for several days after the major syndrome has disappeared, and its return to the original level may be best appreciated by counting the night heart rate when the patient is asleep. It is at such times that the accelerator influences over the heart are in abeyance. Whereas during the seizure of asthmatic breathing with hemoptysis, the heart rate remains high even during sleep, when the attack subsides, the heart rate may be high during the waking hours but under 60 beats per minute during sleep. Irregularities in the heart rhythm have not been observed prior, during, or subsequent to any of the seizures.

Cough and Hemoptysis.—The most striking and alarming feature of these episodes is the blood spitting that appears shortly after the onset of difficulty in breathing which is ushered in at the same time as the palpitation of the heart. At first the respirations are merely increased. Within a short time the expirations become prolonged, just as in the breathing of asthmatic patients when only sibilant and sonorous râles are heard over both chests. Paroxysmal coughing with mild blood spitting usually follows, and unless the blood is brought up from the lungs with each coughing paroxysm, it may be reflexly swallowed as it spills over from the trachea into the pharynx. This has been observed to occur without the patient's knowledge during sleep. The evidence that such a seizure has taken place during a patient's sleep is obvious when irritability of the stomach follows its overflowing, and the swallowed blood from the lungs is vomited in large quantities as brownish coffee-ground material.

The first expectorated transudate from the lungs may be the frothy type of red-tinged sputum that is seen so often in patients with mild attacks of pulmonary edema, a condition which, like profuse hemoptysis, may also occur paroxysmally in patients with mitral stenosis.⁸ This state may last several hours and finally end in a profuse and abundant bright red hemorrhage, varying in quantity from one hundred to several hundred cubic centimeters. Whereas "heart failure cells" are easily

seen in the expectorated material during the milder seizures, when the bleeding is abundant, only red cells and fibrin are seen on the microscopic examination. We have never observed any clots brought up with the sputum, and the streaking may stop as suddenly as it is ushered in.

With the appearance of the blood, the physical signs in the lungs change and may be very variable from hour to hour, depending upon the severity and the duration of the seizure. Dullness with diminished breath sounds may be at first localized to only one part of the chest, the upper right chest being the most common site and the most frequently involved. Later, as the attack is prolonged, the signs may extend to both lungs, anteriorly and posteriorly, and now the râles become large, moist, and bubbling, and appear very near to the ear.

On only one occasion was there noted a temperature increase to 101° F., and this lasted for two days. Localized friction sounds, such as are heard so frequently in infarction of the lung with pleural involvement, are absent, as is the localized sharp pain which often accompanies the development of these.

The X-ray Signs.—The usual roentgen ray findings in the average patient with moisture in the lungs is well known.⁹ Stasis in the lungs is characterized by an increase in the hilar shadows, which in the presence of mitral stenosis assumes the form of a capital H with both limbs of the H extending upward and downward from the root of the lung toward the periphery. In some there is an increase in the density of perivascular tissues, and in the further advanced cases the lungs have the mottled appearance seen so frequently in miliary tuberculosis. Often there is thickening of the pleura from some previous inflammation which is seen on the films as darker shadows along the edges of the lungs; and occasionally a still denser shadow at the bases, in particular at the left base, has been found associated with atelectasis from compression of the bronchus by an enlarged left auricle. In addition to such signs there may be superimposed upon the lung fields of patients with blood-spitting episodes, diffuse shadows extending from the hilum toward the periphery, often mistaken for infiltrations within lung parenchyma due to pneumonia. The transudates in the alveoli may be localized, at such times, to only one part of the lung field, often restricting themselves to one lobe, and may remain so until the end of the attack. These shadows have also been mistaken for localized interlobar effusions when the exudate involved the areas adjacent to the interlobar fissure. All of these shadows have been seen to disappear within a few days after their development without leaving any traces in the lung fields to indicate the widespread involvement observed previously.

The most common differential diagnosis in which the x-ray shadows may shed some light on the underlying pathological lesion responsible for blood spitting is that of infarction of the lung, in which a wedge-

shaped density is often found to spread from the hilar region toward the periphery, well demarcated from the rest of the lung tissue. In such cases, however, the clinical manifestations of pain, fever, leucocytosis, and jaundice are often more reliable than the roentgen ray evidence.

Treatment.—It has been impossible to prevent the onset of such seizures in any of our patients. Once the attack sets in, the adequate use of morphine sulphate as a sedative, with repeated injections of atropine sulphate, has helped to dry up the secretions and allay the apprehension that is always present. With all this, however, death has taken place from asphyxia when the attack has been very severe, although we have not observed death to occur in the actual process of the hemorrhage.*

Pathology and Pathogenesis.—Very recently an attempt has been made by Proft⁷ on the basis of very meager pathological findings, to separate patients with heart disease and severe hemoptyses into two distinct groups. In the first, in which no bleeding point is found within the lung parenchyma or its vessels, the hemorrhage is considered the result of the sudden dilatation of the lung capillaries with diapedesis in the alveoli. Although such patients have heart failure cells in their sputum, peripheral manifestations of congestive heart failure, such as hepatic enlargement and anasarca, are usually absent. In the second group with peripheral stasis, Proft attributes the bleeding to marked dilatation of the capillaries lining the small bronchioles and the possibility of rhexis or rupture of these is held to account for the symptoms and signs that follow.

Our own pathological observations have revealed the lungs following such hemorrhages to be large, fleshy, and firm. On squeezing them, blood could be easily expressed. The cut sections were red and homogeneous. The bronchi and trachea showed marked engorgement and the alveolar capillaries were tremendously congested. No ruptured vessels were seen either grossly or microscopically in many sections obtained from these lungs. In the absence of any embolic or thrombotic manifestations, the most plausible cause for the bleeding at present seems to be that of diapedesis. The immediate factors responsible for initiating this mechanism periodically in recurring forms in such patients as we have described above merits further attention and study.

SUMMARY AND CONCLUSIONS

1. Severe paroxysmal pulmonary hemorrhages, not due to intrinsic disease of the lungs, are uncommon in patients with mitral stenosis. Three cases are reported of young adults under thirty years of age, suffering from chronic rheumatic cardiovalvular disease with mitral

*The prognosis in the few cases we have observed has been poor, as most of the cases have died within a few years of the onset of the hemoptyses. One boy is still living a little over two years after the appearance of such attacks.

stenosis, whose main presenting symptoms were recurrent attacks of pulmonary hemorrhages.

2. These attacks were characterized at times by an "aura" with psychogenic manifestations, severe pains between the shoulder blades, and palpitation of the heart. In one patient an urticarial rash ushered in the seizures.

3. The onset of these attacks was usually during an afebrile period and came on many years after the first evidence of rheumatic fever.

4. The attacks themselves were characterized by dyspnea, pain, asthmatic breathing, cough, and hemoptysis. At first the expectoration was frothy in nature, but later there were frank hemoptyses in quantities of from one to several hundred cubic centimeters of blood.

5. The lungs during such seizures showed evidences of either localized or diffuse transudation in the alveoli, and there was a characteristic x-ray picture that was often mistaken for pneumonia. The attacks would last from one hour to several days, and with their cessation the lung signs cleared up entirely.

6. It was impossible to prevent the onset of such seizures in these patients by any medication. Morphine sulphate and atropine sulphate administered in adequate doses following the seizures seemed to allay the fear and abate the hemoptysis.

7. Two of these patients died within three years following the onset of such recurrent episodes. In the one case with autopsy no bleeding point could be found.

8. It is probable that in the absence of any embolic or thrombotic manifestations in the lungs, such seizures are the result of some reflex stimulation of the capillaries lining the alveoli, resulting in hemorrhages from diapedesis, or possibly also from rhexis of capillaries lining the walls of the bronchial tree.

(For discussion see p. 113.)

REFERENCES

1. Sée, G.: *Traité des Maladies du Cœur*, Paris, 1889, p. 102.
2. Vermullen, P.: *Haemoptysie Cardiaque*, Thèse de Paris, 1875.
3. Hoffman, F. A.: Die Bedeutung der Herzfehlerzellen, *Deutsch. Arch. f. klin. Med.* 45: 252, 1889.
4. Schwartz, G.: Ueber einen Fall von abundanten Lungenblutung bei Mitralstenose und hochgradiger Sklerose der Arteria Pulmonalis, *München. med. Wehnschr.* 54: 333, 1928.
5. Duken, J.: Profuse Lungenblutungen bei recidivierende Endocarditis und Polyarthritis im Kindesalter. Zugleich ein Beitrag zur Kenntniss der kindlichen Mitralstenose, *Ztschr. f. Kinderh.* 45: 333, 1928.
6. Hoffman, A.: Nichttuberkulose Lungenblutungen, *Deutsch. med. Wehnschr.* 52: 1581, 1926.
7. Proft, A.: Ueber die Quellen starker Lungenblutungen bei Stauungslungen, *Ztschr. f. klin. Med.* 119: 218, 1932.
8. Gallavardin, L.: De l'oedème pulmonaire aigu dans les cardiopathies valvulaires endocardiaques en dehors de la gravidité; insuffisance ventriculaire et insuffisance auriculaire gauche, *Arch. d. mal. du cœur* 14: 262, 1921.
9. Zdansky, E.: Beiträge zur Kenntniss der kardialen Lungenstauung auf Grund röntgenologischer, klinischer und anatomischer Untersuchungen, *Wien. Arch. f. inn. Med.* 18: 461, 1929.

A CLINICAL CONCEPTION OF RHEUMATIC HEART DISEASE*

SAMUEL A. LEVINE, M.D.

BOSTON, MASS.

MOST physicians are still of the opinion that the cause of rheumatic fever or rheumatic heart disease is unknown. It is true that of all infectious agents the streptococci have been studied most arduously and that they are apparently more intimately related to rheumatic fever and its various accompaniments, than other microorganisms. Despite these painstaking bacteriological efforts, on critical analysis it cannot be said that streptococci cause rheumatic heart disease; however, such infections may aggravate the rheumatic condition. Similarly, one may say that the diligent search and removal of foci of infection has proved far from effective either in preventing or in ameliorating the terrible ravages of the disease. With the situation as it stands, recognizing the great importance of continued study of the bacteriological aspects of the question, there is another phase of the problem that I feel has not received sufficient attention. I refer to the condition of the host or patient, the internal environment in which the disease develops, and especially the possible rôle the glands of internal secretion may be playing.

The response of the human body to outside influences is very variable and difficult to predict. This is true whether the offending agent is a physical, chemical, or infectious cause, or whether it is a psychic trauma. It is common knowledge that one individual may lose his entire business and as a result commit suicide, while another merely smiles and starts right over again. One jilted suitor becomes depressed, another takes to drink and a third laughs it off. So it is with infectious diseases. A luetic infection develops into a stubborn dermatological syphilide in one case and in another may show very little skin and a great deal of early nervous system involvement, as if the infection had taken a direct route to the brain and meninges. We have been too ready to ascribe these differences to variations in the virulence or specific type of the invading organisms. On the other hand, there is much to make us believe that the peculiarity of the patient may have a great deal to do with these inexplicable phenomena. Not only do human individuals differ from each other, but we differ from year to year and from month to month in our bodily behavior, in our physical, anatomical, and chemical make-up, and presumably in our biological reactions to bacteriological invasions. Some extremely important observations in this regard were published by Brown¹ and his coworkers. He found that in rabbits there were con-

*Read before the American Heart Association, Milwaukee, Wisconsin, June 13, 1933.

siderable differences in the relative weight of the different organs of the body during different months of the year. This was particularly true of the endocrine glands. It is reasonable to assume that similar seasonal variations occur in human beings. By this is meant that we have a greater or lesser amount of thyroid or pituitary gland in proportion to the entire body weight at one time of the year than at another. Similar changes in the chemical constituents of the blood, such as calcium, phosphorus, lecithin, and cholesterol, were also observed. The purpose of this communication is to call attention to the possibility that such changes in balance in the internal environment of the human body may have a direct bearing on the problem of rheumatic fever.

The causative agent of rheumatic fever is probably very prevalent in certain parts of the world. Notwithstanding this great prevalence and the failure to develop lasting immunity to recurrences (for the very opposite is characteristic of the disease), only a small part of the population develops this disease. It seems likely that many if not all are exposed to the infection, certainly if the streptococci have much to do with it. Is it not reasonable to assume that the condition of the individual host determines whether the disease develops and what form it will take? One child gets the infection and manifests it in the form of St. Vitus' dance, another polyarticular rheumatism, a third skin lesions, a fourth may show none of these lesions and respond purely with a pericarditis, and a fifth may only have a slight fever, sweats, and anemia without gross cardiac or arthritic involvement. Furthermore, in the same person the internal environment may be in such a state that during one month or one year he may have chorea and at another rheumatism. Such variations I do not believe can be ascribed to changes in the infectious agent but are more likely due to changes in the host.

A very striking observation with regard to chorea illustrates the general thesis presented above. Whereas chorea very commonly lasts for months and tends to recur at times over a period of years, one practically never sees chorea in patients over twenty years old, except under one circumstance and that is in a pregnant woman. Here again pregnancy fundamentally alters the internal environment of the patient, especially the endocrine balance. It is more reasonable to assume that this altered state of the internal environment is responsible for the peculiar recurrence of this disease at this time, than to suppose that the infectious agent just happened to become reactivated during pregnancy. A further illustration is the occurrence of so-called "growing pains." We all frequently see these children with recurrent pains in the limbs during their early years, which disappear as full growth is established. The term "growing pains" attains more than colloquial significance when it is viewed in the light that the rheumatic pains disappear and the dis-

case is held in check when the proper endocrine balance, possibly determined in this instance by the pituitary gland, has been established.

Another peculiarity of rheumatic fever is of interest in relation to the internal environment of the host, i.e., the familial incidence of the disease. It is obvious that children of the same family are exposed to the same surroundings—food, climate, and hygienic conditions. These factors and the spread of infection by contact no doubt are important in producing a high familial incidence of the disease. I do not think, however, that this is the entire explanation. There must be an additional hereditary factor of vascular vulnerability. The following experiences throw some light on this question. A husband and wife died of coronary artery disease. Among their children three developed hypertension in the thirties or early forties. In each instance there has already been one child (a grandchild of the original anginal grandparents), with rheumatic fever or chorea. These three rheumatic children have lived in entirely different localities, one in New Hampshire and the other two in different parts of Massachusetts, and see each other but rarely. It hardly seems that contact or environment are adequate to explain this. Likewise, a little boy, eight years old, previously perfectly well, developed chorea during the month of February. His mother, a most intelligent person, mentioned as a curious fact that her brother about twenty-five years previously had had the same disease (chorea) at the same age (eight), and at the same month of the year (February). It is unlikely that these four variables, disease, age, month, and family should occur together by mere chance. In the light of the work of Brown previously mentioned, it is probable that the endocrine or biological state of that boy, which he inherited from his mother, was just appropriate at that time to develop the disease just as happened to his uncle. These and similar experiences form a background that is not at all new but which deserves more intensive consideration and emphasizes the importance of the host in the development of rheumatic heart disease. The problem lends itself somewhat to experimentation inasmuch as the progress in endocrinology has been considerable during the past decade. At present numerous hormones of the glands of internal secretion are available, so that the effects of either an increase or decrease in their functions may be studied in relation to the susceptibility to disease. There is reason to hope that such investigation will prove fruitful in throwing light on methods of prevention and treatment of rheumatic heart disease.

(For discussion see p. 112.)

REFERENCES

1. Brown, W. H.: Constitutional Variation and Susceptibility to Disease, *Arch. Int. Med.* 44: 625, 1929.

RHEUMATIC MANIFESTATIONS IN SUBACUTE BACTERIAL ENDOCARDITIS IN CHILDREN*

O. SAPHIR, M.D., AND S. A. WILE, M.D.

CHICAGO, ILL.

A POSSIBLE relationship of subacute bacterial endocarditis to rheumatic fever† has long attracted the attention of workers in this field. At present, some believe that these two conditions are different diseases and others that they are merely different manifestations of the same disease. Since subacute bacterial endocarditis and rheumatic fever are not infrequently closely associated, a clinico-pathological study of the two diseases, when occurring in the same individual, seemed to offer a method of investigation which might aid in a better understanding of their possible relationship.

It is sometimes difficult to make a differential diagnosis between rheumatic fever and subacute bacterial endocarditis. At times the clinical picture of the former merges almost imperceptibly into that of the latter. As a rule, however, there are certain essential differences. In rheumatic fever, endocarditis is but one manifestation of a general process, while in subacute bacterial endocarditis the valvular infection is the essential seat of the disease. It has been noted that rheumatic fever occurs chiefly in the first two decades of life while subacute bacterial endocarditis occurs more often after the second decade (Thayer³). It has been said repeatedly that subacute bacterial endocarditis rarely occurs in patients with mitral stenosis or auricular fibrillation (Rothschild et al.,⁴ and Levine⁵) which are among the common manifestations of rheumatic heart disease. It is known that subacute bacterial endocarditis at times develops long after the clinical evidence of an active rheumatic infection has subsided. Finally, the etiology of rheumatic fever is unknown, while *Streptococcus viridans* is usually demonstrable in blood cultures taken from patients with subacute bacterial endocarditis. In spite of such apparent differences which can be recognized clinically, it is generally emphasized that a heart valve which has been the seat of rheumatic endocarditis may later become involved in subacute bacterial endocarditis.

*From the Department of Pathology of the Nelson Morris Institute of the Michael Reese Hospital and the Sarah Morris Hospital for Children, Chicago.

Aided by a grant from the Albert Kuppenheimer Fund.

Read in part at the Ninth Annual Scientific Session of the American Heart Association in Milwaukee, Wisconsin, June 13, 1933.

†We fully realize the inadequacy of the terms rheumatic fever, rheumatic infection, rheumatic arthritis, etc. But because the more recently used terms, such as rheumatismus infectiosus specificus (Griffith¹), rheumatic granulomatosis (Fahr²), etc., also do not express the essential of what is generally known as rheumatic fever, we decided to use the old terminology which at least has the advantage of more common usage.

TABLE I

NO.	AGE	SEX	HISTORY OF PREVIOUS RHEUMATIC INFECTION	NUMBER OF RECURRENCES	TIME INTERVAL BETWEEN RECURRENCES	TIME INTERVAL FROM LAST RHEUMATIC MANIFESTATION TO ONSET OF SUBACUTE RAC. END.	HISTORY OF PREVIOUS HEART INVOLVEMENT	DURATION OF LIFE	CAN ONSET OF S.B.E. BE DIFFERENTIATED FROM LAST RHEUMATIC INFECTION
1	10 yr.	M	Acute polyarthrits	3	Varied from 1 to 1½ yr.	5 mo.	Yes	3 yr.	No
2	13 yr.	M	Acute polyarthrits joint and muscle pains	Repeated	Varied from 4½ yr. to 4-5 wk.	2 wk.	Yes	7 yr.	No
3	5½ yr.	M	Acute polyarthrits Sore throats	1		5 mo.	Yes	1½ yr.	Yes
4	17 yr.	M	Acute polyarthrits Fleeting pains	Repeated	Varied from 4 yr. to 6 mo.	7 mo.	Yes	6½ yr.	Yes
5	19 yr.	F	Acute polyarthrits	2	9½ yr.	3 mo.	Yes	10 yr.	No
6	19 yr.	F	Acute polyarthrits	1		10½ yr.	Yes	11 yr.	Yes
7	5 yr.	M	Swollen joints following acute infection	1		4 wk.	No	4 wk.	No
8	13 yr.	M	Sore throats Fleeting joint pains	Repeated	Varied from few wk. to several mo.	2 wk.	No	Ago of onset unknown	No

TABLE I—CONT'D

NO.	AGE	SEX	HISTORY OF PREVIOUS RHEUMATIC INFECTION	NUMBER OF RECURRENCES	TIME INTERVAL BETWEEN RECURRENCES	TIME INTERVAL FROM LAST RHEUMATIC MANIFESTATION TO ONSET OF SUBACUTE BAC. END.	HISTORY OF PREVIOUS HEART INVOLVEMENT	DURATION OF LIFE	CAN ONSET OF S.B.E. BE DIFFERENTIATED FROM LAST RHEUMATIC INFECTION
9	11 yr.	F	Sore throats	Repeated	Varied from 3-6 mo.	5 yr.	Yes	8 yr.	Yes
10	14 yr.	F	Sore throats Fleeting joint pains	Repeated	Varied from few wk. to several mo.	Unknown	No	Age of onset unknown	Yes
Summary			In all cases	3 cases had 1 attack, 1 case had 2 attacks, 1 case had 3 attacks, 5 cases had repeated attacks	Few weeks to 9½ yr.	2 wk. to 10½ yr.	In 7 cases	4 wk. to 11 yr.	5 yes 5 no
				3 cases had 1 attack, 3 cases had 2 attacks, 3 cases had repeated attacks	Few weeks to 7 yr.	2 wk. to 3 yr.	In all cases	2 mo. to 9½ yr.	
10 rheumatic cases			In 9 cases						

Up to the present time, most of the observations on a relation between subacute bacterial endocarditis and rheumatic fever have been made in adults. This is probably due to the fact that until a few years ago subacute bacterial endocarditis in children was thought to be extremely rare (Blumer⁶). In adults, a rheumatic infection may antedate by a long period of time the death which results from subacute bacterial endocarditis. Consequently, any association between these two conditions may have become obscured.

We selected for study cases of subacute bacterial endocarditis occurring in children. A study of the clinical histories of these children, together with gross and histological examinations of the hearts, was undertaken in order to see if there existed evidence of a preceding or coincident rheumatic infection, and, if so, whether any relationship between the two diseases could be established. In children the time interval between a possible rheumatic infection and the subacute bacterial endocarditis would necessarily be shorter than in adults.

Our series comprises 10 cases of subacute bacterial endocarditis. Eight were children and 2 in the early adolescent period who had been under observation since childhood.* The clinical diagnosis of subacute bacterial endocarditis was confirmed in each case at autopsy. Six of this group were males and 4 were females; the ages ranged from five years to the young adolescents, both of whom were nineteen years old. In 6 of the 10 patients we were able to obtain a clear-cut history of a preceding rheumatic polyarthritis; 3 other patients gave a history of frequent sore throats and fleeting joint pains which might be interpreted as evidence of a rheumatic infection. In another patient there was a history of transient joint swellings following an acute infection, diagnosed as measles. None of the children gave a history of chorea, and subcutaneous nodules were present in only one patient. Table I gives a summary of the significant clinical findings of our patients. It also summarizes the comparable clinical findings in 10 other children dying of rheumatic heart disease, used as controls.

Of the 6 patients with a definite history of previous rheumatic polyarthritis, 2 had only one attack, 1 had two, 1 three, and 2 others had repeated attacks. Of the 2 patients with only one attack, the time interval between the rheumatic polyarthritis and the appearance of clinical signs of subacute bacterial endocarditis was five months in one and nine and one-half years in the other. In the 2 patients who had two and three attacks of polyarthritis, the time interval between the last attack and the clinical onset of subacute bacterial endocarditis was three months and five months respectively. Of the 2 patients who had repeated attacks of polyarthritis, the last attack antedated the clinical

*We are indebted to the Attending Staff of the Sarah Morris Hospital for the use of these cases.

picture of subacute bacterial endocarditis by seven months in one, while the other had an acute polyarthrititis two weeks before the clinical signs of subacute bacterial endocarditis appeared. Of the 4 patients who did not have a definite history of rheumatic polyarthrititis, 1 revealed clinical evidence of subacute bacterial endocarditis five years after the occurrence of the last probable clinical rheumatic manifestation, 1 developed acute polyarthrititis shortly after admission to the hospital and four weeks later the first clinical signs of subacute bacterial endocarditis appeared, another had transient joint swellings three weeks before the appearance of the clinical signs of subacute bacterial endocarditis and in the remaining patient, no time relationship could be established and clinical evidence of bacterial endocarditis developed after a long period of time during which the patient was apparently well. In the 7 patients who had more than one attack of a clinically active rheumatic infection, the time between the attacks varied greatly. Five of these 7 patients had repeated attacks at intervals varying from a few weeks to several months. In 2 of these patients, there had been an interval of four years during which time there was apparently no clinically active rheumatic infection. In the 2 cases with two and three attacks respectively the time between the attacks was nine and one-half years in the first instance and one to one and one-half years in the latter. In 5 of the 9 patients in whom the time interval between the last rheumatic manifestations and the appearance of clinical signs of subacute bacterial endocarditis could be estimated, the actual onset of the subacute bacterial endocarditis could not be determined. The onset of the final illness was similar in every respect to the preceding attacks of acute rheumatic infection and gradually merged into the clinical picture of subacute bacterial endocarditis. The duration of life from the first clinical evidence of an active rheumatic infection varied from four weeks to eleven years.

Eight of our patients had had previous tonsillectomies. In 6 of these the tonsils had been removed from one to seven years prior to the onset of clinical evidence of a rheumatic infection. In 2 patients tonsillectomies had been done one year and five months respectively after the onset of the first attack of acute polyarthrititis. Of these 2, 1 had repeated attacks of acute polyarthrititis after tonsillectomy while the other had only one attack. Tonsillectomy seemed to have no bearing in our cases on the development of a clinically active rheumatic infection or on the development of subacute bacterial endocarditis.

In 7 of our patients, the rheumatic infection was known to have involved the heart, while in 3, heart disease was first noted on admission to the hospital. Clinically, the mitral valve alone was thought to be involved in 4 instances, and the mitral and aortic valves in the remaining 6. *Streptococcus viridans* was obtained in blood cultures taken from all 10 patients.

From an analysis of the clinical records of these patients it seems evident that neither the number of preceding rheumatic attacks, the time interval between the attacks, nor the length of time elapsing from the last clinical manifestation of an active rheumatic infection to the clinical onset of subacute bacterial endocarditis is of any special significance in regard to the development of subacute bacterial endocarditis.

For comparison we analyzed the clinical records of 10 other children dying of uncomplicated rheumatic heart disease. The diagnosis in each instance was verified at autopsy. In this group, 9 gave a history of a preceding rheumatic infection. Three had one attack, 1 two, 1 three, and 5 had repeated attacks. The time between the attacks varied from two weeks to seven years. The time interval from the last evidence of an active rheumatic infection to the onset of the final illness varied



Fig. 1.—Subacute bacterial endocarditis of the mitral valve. Note the size of the vegetations, the involvement of the auricular endocardium, and the thickened chordae tendineae.

from two weeks to three years. The duration of life from the first evidence of an active rheumatic infection varied from two months to nine and one-half years. It is obvious that the number of rheumatic attacks, the interval between attacks, the time elapsing from the last attack to the onset of the final illness, and the duration of life are similar in those children studied who have had a rheumatic infection and finally developed subacute bacterial endocarditis and in those who subsequently died of uncomplicated rheumatic heart disease.

An autopsy was performed in all of our 10 cases of subacute bacterial endocarditis. These hearts showed the typical lesions of subacute bacterial endocarditis. In addition to large vegetations on the valves and the mural endocardium, various degrees of thickening were found in the valvular areas. Without giving a detailed description of the gross heart

findings, it can be stated briefly that the mitral valve alone was affected in 4 instances and the aortic and mitral valves together in 4. In one instance, the mitral and tricuspid valves were involved and in another the mitral, aortic, and pulmonic valves. In four of the ten hearts, there was evidence of moderate stenosis of the mitral orifice. Sections of the vegetations on the valves showed gram-positive cocci in every instance.

The histological examinations of the myocardium revealed various changes. Small abscesses were found in some of the hearts. In others, there were accumulations of lymphocytes and endothelial cells, partly within the parenchyma and partly within the interstitial tissue. In some instances, large areas consisting of a proliferation of connective

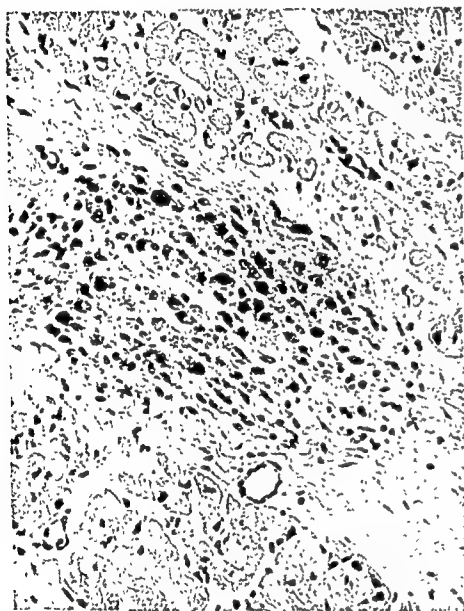


Fig. 2.

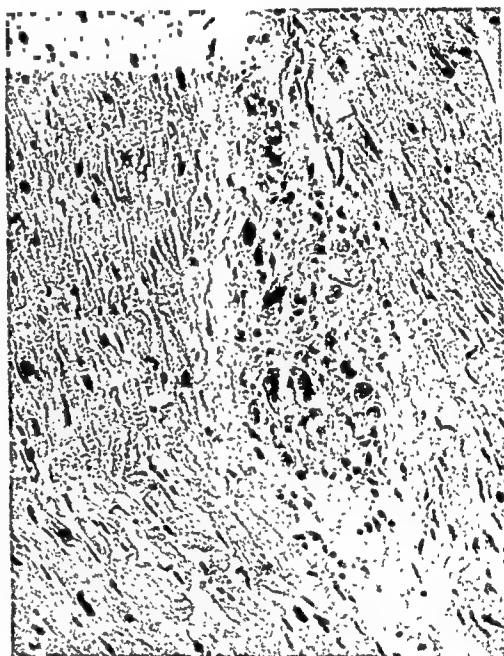


Fig. 3.

Fig. 2.—Aschoff body in the myocardium.* (Hematoxylin-eosin preparation) ($\times 350$).

Fig. 3.—Aschoff body in the myocardium. Note the multinucleated cells. (Iron-hematoxylin preparation) ($\times 450$).

tissue cells were seen, with a few newly formed connective tissue fibers, small blood vessels, and occasional lymphocytes. These areas were found interrupting the course of the heart muscle fibers. Simple fibrosis, perivascular in distribution, was often encountered.

In addition to these changes, typical Aschoff bodies were found in every instance. We wish to emphasize that whenever there was doubt whether or not a lesion was an Aschoff body, it was not diagnosed as such. Gross⁷ has recently taken a similar attitude. Cellular infiltrations resembling Aschoff bodies were not included. The Aschoff bodies

*Compare Figs. 2 and 3 with Figs. 4, 5, 6, and 7, and note the morphological differences between typical Aschoff bodies and experimentally produced nodules, subcutaneous rheumatic nodules, etc.

invariably consisted of infiltrations of large cells often showing a basophilic cytoplasm containing one, two, or three nuclei, a few lymphocytes, and an occasional plasma cell and polymorphonuclear leucocyte. These accumulations of cells were almost always found in the vicinity of the blood vessels. Occasionally, necrotic foci or a fibrin-like material were encountered in these areas. The large cells were seen in parallel rows, often assuming a typical palisade arrangement. The internal structure of the nuclei of some of these cells could be compared with that of a spider web. Apparently depending upon the pressure of the surrounding tissues, the cells were either compactly arranged, the Aschoff bodies presenting an elongated appearance, or the cells were well separated from one another, the Aschoff bodies appearing rather square or round. Since a discussion of the origin of the large cells would far exceed the scope of this communication, we merely wish to state that we believe that these cells are polyblasts rather than myocytes. The various routine stains for bacteria did not reveal microorganisms within the Aschoff bodies.

We are well aware of the discrepancy of opinion as to what constitutes an Aschoff body. This was brought forward at the relevant discussion during the conventions of the Association of the American Pathologists and Bacteriologists in 1929 and 1930. This discrepancy of opinion is due to differences in the criteria used for identifying Aschoff bodies. These variations in criteria apparently result from the fact that some authors (Klinge,⁸ Klinge and Vaubel⁹) believe that an Aschoff body may undergo changes and various stages of development, losing some characteristics and gaining others. We must emphasize, however, that in our opinion, the Aschoff body is unquestionably recognizable in one stage only. This is the one we have described. Structures, presumably Aschoff bodies in different stages of development, if they occur at all, should be classified under the broader term of "structures resembling Aschoff bodies." We fully realize that we may fail to recognize some Aschoff bodies, and thus fail to make a diagnosis of rheumatic myocarditis, if we use such rigid criteria for identification. On the other hand, we will be less likely to err in considering cellular infiltrations resembling Aschoff bodies as true Aschoff bodies. The accompanying pictures are characteristic, and only when the cellular infiltration conforms to such a picture do we believe we are justified in designating the structure an Aschoff body. It may be of interest to quote Thayer¹⁰ who stated, "The focal perivascular Aschoff bodies are quite characteristic and unlike anything that we have seen under other circumstances. They appear to be distinctive of acute rheumatic heart disease."

It may be added that it is sometimes difficult to determine whether some authors consider rheumatic nodules, and Aschoff bodies in the myocardium identical or different structures. Clawson¹¹ uses these terms

interchangeably, and Sacks¹² stated, "Pathologists are generally agreed upon the fundamental histological similarity between the subcutaneous rheumatic nodules and the Aschoff bodies." From our experience, however, we have come to the conclusion that the Aschoff body found in the heart and occasionally in other tissues, and the rheumatic nodules found in the subcutaneous tissue, are morphologically different structures. The latter is a nonspecific tissue inflammation somewhat resembling Aschoff bodies, the former—as will be pointed out later—is more likely a specific tissue reaction. To avoid any confusion we have used the term Aschoff body exclusively for the specific lesion found in the myocardium.

So far, we have been able to show that in 8 children and 2 in the adolescent period dying of subacute bacterial endocarditis, clinical evidence of a preceding rheumatic infection was present in every instance. All cases at autopsy revealed typical Aschoff bodies within the myocardium and valvular changes characteristic of subacute bacterial endocarditis.

DISCUSSION

It seems to us that there are three possible explanations for these two findings: (1) A coincidental occurrence. (2) Both conditions may be manifestations of the same disease, differing only in the immunological response of the individual. (3) Both conditions may be related so far as the injury due to a previous rheumatic infection may predispose the valve to a subsequent subacute bacterial endocarditis.

Regardless of the possible theories of a cause and effect relation between rheumatic fever and subacute bacterial endocarditis, a coincidental occurrence cannot be ruled out. We have no proof for the assumption that rheumatic fever and subacute bacterial endocarditis may run a parallel course in the same patient without any causative relation to one another. Neither can we conclusively disprove a coincidental occurrence. We can merely say that such a coincidence seems to us quite unlikely.

Allergy is an attractive explanation of rheumatic fever and subacute bacterial endocarditis; but at best it is an hypothesis founded on animal experiments and theories which still remain to be proved. Swift¹³ stated that the experimental demonstration of the hypersensitive and immune types of reaction toward streptococci seems transferable by analogy to the clinical conditions of patients with rheumatic fever and with subacute streptococcus endocarditis respectively. The difference in the diseases is supposed to lie in the difference of the reaction of the host.

Since rheumatic fever has been considered an allergic phenomenon, the significance of the Aschoff body has aroused much discussion among the workers in this field. Some still believe in the specificity of the Aschoff body, while others deny this and regard it merely as a non-specific (hyperergic) reaction. It seems clear to us that the supporters

of the allergic theory must dispose of the Aschoff body as the specific histological entity of rheumatic myocarditis. Otherwise, they cannot assume that the Aschoff body merely signifies an hyperergic reaction of the patient toward a nonspecific cause. It must be postulated, however, that in order to disprove the specificity of the Aschoff body, unquestionable Aschoff bodies must be produced experimentally. Although it is claimed by some authors that they have been able to produce Aschoff bodies experimentally in previously sensitized animals and in others not sensitized, in our opinion this has not yet been accomplished. To judge from the reproductions of the histological sections shown by these various authors, it should be pointed out that the experimentally produced inflammatory exudate, though morphologically resembling an Aschoff body, is in no instance typical of one. We firmly agree with Aschoff¹⁴ who, during a discussion of this subject in 1925, stated that the lesions



Fig. 4.

Fig. 4.—Picture taken from Klinge and Vaubel's article.⁹ Called: Typical Aschoff body with giant cells in intima of aorta.

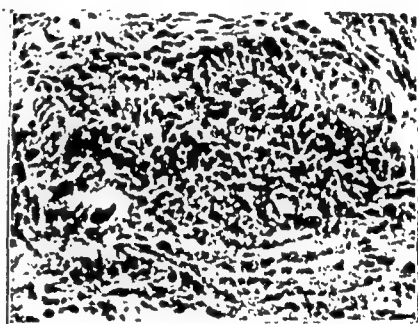


Fig. 5.

Fig. 5.—Picture taken from Swift's article.¹³ Called: Subcutaneous rheumatic nodule showing intense proliferation of fixed cells around groups of blood vessels.

in question are beautiful examples of hyperergic inflammation but are not typical of Aschoff bodies. Four years later, Aschoff¹⁵ again warned against considering the histological changes found in instances of anaphylactic shock analogous to the nodules seen in rheumatic fever. It should also be mentioned that the few reports of the presence of Aschoff bodies in the hearts of patients dying from diseases other than rheumatic fever are used as further evidence against the specificity of the Aschoff body (Siegmund,¹⁶ Clawson,¹¹ v. Müller¹⁷). It still remains to be proved, however, whether these lesions were Aschoff bodies and, if so, whether the patients had not had a previous rheumatic infection and the Aschoff nodules were anatomical evidence of a rheumatic myocarditis. A similar criticism was made recently by Fahr.¹⁸ It might be of interest to mention in this connection that recently Loewe, Gross and

Eliasoph¹⁹ failed in their attempts to reproduce rheumatic disease in animals. As long as the cause of rheumatic fever is not definitely established, as long as typical Aschoff bodies are not demonstrable in conditions other than rheumatic fever, and as long as typical Aschoff bodies similar to those found in human hearts cannot be reproduced experimentally, so long must we regard the Aschoff body—just as we regard the tubercle and gumma as the specific tissue reaction toward the tubercle bacillus and the *Treponema pallidum* respectively—as a specific tissue reaction toward the unknown causative agent of rheumatic fever. We feel that at the present time we are forced to believe that the Aschoff body is a specific granuloma caused by the virus of rheumatic fever, even though it is not yet possible to demonstrate that virus by the use of present-day laboratory facilities. It seems to us that the burden of proof rests upon those who hold that the Aschoff body is the nonspecific reaction of a sensitized tissue toward a nonspecific virus.

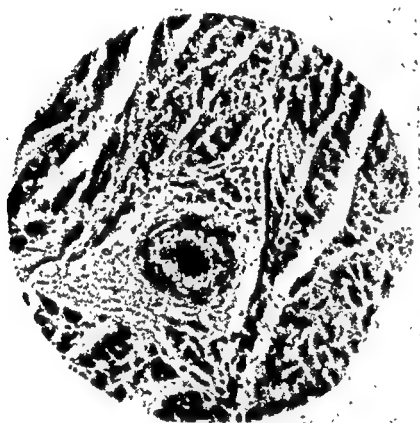


Fig. 6.

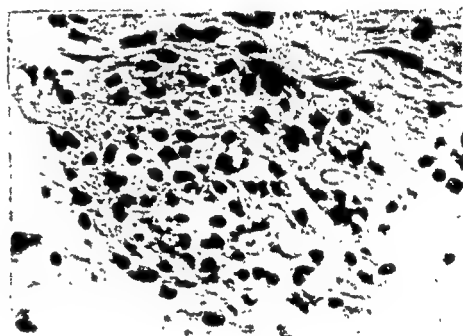


Fig. 7.

Fig. 6.—Picture taken from Klinge's article.²⁵ Called: Granuloma in myocardium in experimentally produced chronic recurrent anaphylactic inflammation.

Fig. 7.—Picture taken from Clawson's article.²⁶ Experimental nodule in subcutaneous tissue of rabbit.

The supposed immune response in subacute bacterial endocarditis as evidenced by skin tests is open to question. Howell and Corrigan²⁰ made skin tests on two patients with subacute bacterial endocarditis. They found the skin tests repeatedly negative in one patient, revealing an immune reaction, while in the other the tests were repeatedly positive. Both cases, as proved by post-mortem examination, were definite examples of subacute bacterial endocarditis. In both instances *Streptococcus viridans* was cultured from the blood and in both instances the skin tests were made with filtrates of these and other bacteria. As this experiment was repeated several times, it seems to show that subacute bacterial endocarditis was not an immune response in at least one of these patients. Since the hypothesis of the immune reaction does not hold in all instances, we do not believe its validity is established.

The finding of typical Aschoff bodies in the myocardium in our 10 cases of subacute bacterial endocarditis seems to us evidence against the assumption that subacute bacterial endocarditis is the immune response in a previously hypersensitive person. It would be difficult to explain why a person should react almost simultaneously in two ways; namely, with a hypersensitive reaction, of which the Aschoff body is supposed to be an example, and with an immune reaction, of which subacute bacterial endocarditis is a paradigm.

The finding of moderate stenosis of the mitral orifice in 4 of our 10 patients is of interest. It has been suggested (Fulton and Levine²¹) that the infrequency of subacute bacterial endocarditis in patients with mitral stenosis is due to the fact that the stenosis results from a progressive rheumatic infection, and consequently there is a persistence of the allergic state. Even in this small group of cases, it appears that the occurrence of subacute bacterial endocarditis in patients with stenosis of the mitral orifice is not as infrequent as one may be led to believe. Very recently, Davis and Weiss²² in an analysis of 47 autopsies on patients dying of subacute bacterial endocarditis found stenosis of the mitral orifice in 12 instances, while in a group of 474 patients showing evidence of rheumatic heart disease this lesion was present 142 times. They concluded that subacute bacterial endocarditis occurs in about the same proportion of patients with mitral stenosis as mitral stenosis occurs in patients with rheumatic endocarditis. They also stated that statistical analysis and morphological findings indicate that any degree of rheumatic endocarditis is equally liable to be the basis of a subacute bacterial endocarditic process. Owing to the relatively large number of rheumatic hearts with mild lesions, instances of subacute bacterial endocarditis occurring with marked mitral stenosis are correspondingly infrequent. The relative infrequency of subacute bacterial endocarditis in patients developing auricular fibrillation might also be explained on this basis.

If we consider a coincidental occurrence or a difference in the immunologic response of a person as unsatisfactory explanations of the relationship between rheumatic fever and subacute bacterial endocarditis, we must then come to the conclusion that a primarily diseased valve mechanically predisposes to a subsequent subacute bacterial infection. This was the prevailing opinion until a few years ago. The most common predisposing factors were thought to be an old rheumatic endocarditis and congenital anomalies of the heart.

The congenital anomalies *per se* were generally considered to form the basis for a subsequent subacute bacterial endocarditis. It may be mentioned in this connection that we have studied 3 cases of subacute bacterial endocarditis superimposed on congenital defects of the heart. No evidence of a preceding rheumatic infection could be elicited from

the history and a careful histological examination of the hearts did not reveal any changes in the valves that could have been interpreted as evidence of a healed endocarditis. The myocardium showed neither Aschoff bodies nor fibrotic changes. It seems obvious that in these three instances the malformation alone predisposed the valves to the subsequent subacute bacterial endocarditis which was similar in every respect to the subacute bacterial endocarditis engrafted upon old inflammatory valvular lesions.

The infrequent association of subacute bacterial endocarditis and insufficiency of the aortic valve due to syphilis (Blumer⁶) is often used as an argument against the susceptibility of primarily diseased valves to subacute bacterial endocarditis. It should be pointed out, however, that the deformity of the aortic valve resulting from any type of endocarditis except that brought about by syphilis, is characterized either by a shortening of the cusps in their longitudinal diameter (insufficiency of the valve) or by adhesions between the lateral portions of the cusps (stenosis of the aortic orifice). In both conditions, we believe that the disfiguration of the valves provides, during their physiological activity, larger areas than normal for the settling of bacteria. A similar condition is found in the most frequent congenital anomaly of the aortic valve which shows a common curtain of two cusps with a slight separation in the region of the sinus of Valsalva (bicuspid aortic valve). The aortic valve in syphilis, however, is characterized by adhesions between the lateral portions of the cusps to the aortic wall of the sinus of Valsalva (Saphir and Scott²³). Such adhesions produce a narrowing of the sinus, spreading of the commissures, and consequent limitation of the excursions of the cusps. We believe that because of the limited excursions of the cusps the area for settling of bacteria in syphilitic aortitis is much less than in the two previously mentioned conditions and offer this explanation for the rarity of subacute bacterial endocarditis being superimposed on an insufficiency of the aortic valve caused by syphilis.

The outstanding anatomical findings in our 10 cases were subacute bacterial endocarditis, older fibrotic lesions in the heart valves, perivascular areas of fibrosis, and Aschoff bodies in the myocardium. The possibility that the same agent which caused the final subacute bacterial endocarditis might also have caused the Aschoff bodies seems unlikely because the vegetations on the valves were loaded with gram-positive cocci while no organisms could be found within the Aschoff bodies. The question naturally arises as to whether the Aschoff bodies were recent and correspond to the onset of the subacute bacterial endocarditis or whether they were older, possibly dating from the primary rheumatic endocarditis. At first it might appear that the Aschoff bodies in our cases had been present since the first rheumatic infection. If, however, the perivascular areas of fibrosis are regarded as fibrous replacements

of Aschoff bodies, it would be difficult to explain why some of them should maintain their characteristic architecture while others undergo fibrosis. It would seem, therefore, that the Aschoff bodies, in at least some of our heart specimens, were recent and indicate a new rheumatic infection which must have been present at the time of the development of the subacute bacterial endocarditis, the old primary rheumatic infection having healed. It is equally possible that the primary rheumatic myocarditis was chronic and slowly progressive in nature, showing a tendency toward healing (fibrosis) with exacerbations (recent Aschoff bodies) still appearing. From an analysis of the clinical histories of our patients, it cannot be definitely determined whether the symptom-free periods indicate that the previous rheumatic infection had healed and the subsequent rheumatic attacks were new infections, or whether the rheumatic infection was chronic and characterized by periods of quiescence and exacerbations. Although in 2 of our patients the long time-interval between the rheumatic attacks would seem to suggest that the subsequent attack was an entirely new infection rather than an exacerbation of a chronic disease, the repeated attacks at a short time-interval in 5 of the 7 patients with more than one attack cause us to feel that the infection is probably chronic and marked by periods of exacerbations. As suggested by Libman,²⁴ it may well be that the development of an intercurrent infection, however mild, may serve to reactivate the quiescent rheumatic infection. The fact that in 5 out of 10 patients the clinical picture of rheumatic fever had gradually merged into a characteristic picture of subacute bacterial endocarditis, might be the clinical parallel to the simultaneous presence of Aschoff bodies and subacute bacterial endocarditis. We believe that as the result of an incidental *Streptococcus viridans* bacteremia, bacteria settled upon the primarily diseased valve. This infection, because of the fact that the valve was primarily diseased, possibly also because the older endocardial and myocardial lesions were chronic and progressive in nature, developed in such a fashion as to lead to the picture of a subacute bacterial endocarditis. The finding of Aschoff bodies is significant because they indicate the rheumatic nature of the primary disease.

SUMMARY AND CONCLUSIONS

A clinico-pathological study of 10 cases of subacute bacterial endocarditis, 8 occurring in children and 2 in young adolescents who had been under observation since childhood, is reported. The clinical histories revealed evidence of a preceding rheumatic infection in every instance. Anatomically, all hearts showed healed endocarditis, subacute bacterial endocarditis, and Aschoff bodies in the myocardium, in addition to other changes. The blood specimens revealed pure cultures of *Streptococcus viridans* and smears taken from the vegetations of the heart valves showed gram-positive cocci arranged in chains.

The relation between the rheumatic infection and the final subacute bacterial endocarditis is discussed. A coincidental occurrence of these two conditions, though not definitely excluded, seems unlikely. Although allergy is an attractive explanation of rheumatic fever and its relation to subacute bacterial endocarditis, evidence is brought forward which seems to us to speak against the possibility of rheumatic fever being an allergic phenomenon and also against the assumption that both conditions are manifestations of the same disease, differing only in the immunological response of the host. At the present time the weight of evidence seems to be that the only relationship between rheumatic fever and subacute bacterial endocarditis is that the injury due to a previous rheumatic infection predisposes the valve to a subsequent subacute bacterial endocarditis.

The status of the Aschoff body is discussed and the conclusion reached that the Aschoff body is a characteristic structure and a specific reaction caused by the unknown virus of rheumatic fever. We feel that circumscribed cellular infiltrations produced experimentally in hypersensitive animals, though morphologically resembling, are in no way characteristic of Aschoff bodies. We urge the use of strict criteria for identification of Aschoff bodies.

The fact that in a number of cases the clinical rheumatic manifestations gradually merged into the picture of subacute bacterial endocarditis may account for the presence of recent Aschoff bodies in the myocardium of our patients dying of subacute bacterial endocarditis.

(For discussion see page 107.)

REFERENCES

1. Gräff, S.: Der Primärinfekt des Rheumatismus infectiosus spezificus, Verhandl. d. deutsch. path. Gesellsch. 26: 206, 1931.
2. Fahr, T.: Beitrag zur Frage der rheumatischen Granulomatose, Klin. Wchnschr. 8: 1995, 1929.
3. Thayer, W. S.: Observations on Rheumatic Pancarditis and Infective Endocarditis, Ann. Int. Med. 5: 247, 1931.
4. Rothschild, M. A., Sachs, B., and Libman, E.: The Disturbance of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, AM. HEART J. 2: 356, 1927.
5. Levine, S. A.: Some Unproved Impressions Concerning the Subject of Heart Disease, New England J. Med. 198: 885, 1928.
6. Blumer, G.: Subacute Bacterial Endocarditis, Medicine 2: 105, 1923.
7. Gross, L.: Discussion of the paper by Gross, L., Loewe, L., and Eliasoph, B.: Am. J. Path. 5: 531, 1929.
8. Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus. II. Mitteilung. Das subakut-chronische Stadium des Zellknötchens, Virchow's Arch. f. path. Anat. 279: 1, 1930.
9. Klinge, F., and Vaubel, E.: Das Gewebsbild des fieberhaften Rheumatismus. IV. Mitteilung. Die Gefäße beim Rheumatismus, insbesondere die "Aortitis rheumatica," Virchow's Arch. f. path. Anat. 281: 701, 1931.
10. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Reports 22: 1, 1926.
11. Clawson, B. J.: The Aschoff Nodule, Arch. Path. 8: 664, 1929.
12. Sacks, B.: The Pathology of Rheumatic Fever, AM. HEART J. 1: 750, 1926.
13. Swift, H. F.: Rheumatic Fever, J. A. M. A. 92: 2071, 1929.

14. Aschoff, L.: Discussion of the paper by Siegmund, H.: Ueber einige Reaktionen der Gefässwände und des Endokards bei experimentellen und menschlichen Allgemeininfektionen. *Verhandl. d. deutsch. path. Gesellsch.* 20: 260, 1925.
15. Aschoff, L.: Discussion of the paper by Klinge, F.: Experimentelle Untersuchungen über die gewebliche Überempfindlichkeit der Gelenke (Zur Pathogenese des Rheumatismus), *Verhandl. d. deutsch. path. Gesellsch.* 24: 13, 1929.
16. Siegmund, H.: Veränderungen des Herzens und der Gefässe bei septischem Scharlach, *Verhandl. d. deutsch. path. Gesellsch.* 26: 231, 1931.
17. v. Müller, F.: Discussion of the paper by Dürek, H.: Die Periarteriitis nodosa im Rahmen der Allgemeininfektion, *München. med. Wehnschr.* 78: 173, 1931.
18. Fahr, T.: Discussion of the paper by Klinge, F.: Experimentelle Erzeugung von Arthritis deformans, *Verhandl. d. deutsch. path. Gesellsch.* 26: 216, 1931.
19. Gross, L., Loewe, L., and Eliasoph, B.: Attempts to Reproduce Rheumatic Disease in Animals, *Am. J. Path.* 5: 530, 1929.
20. Howell, K. M., and Corrigan, M.: Skin Reactions With Bacterial Filtrates of Anhemolytic Streptococcus, Hemolytic Streptococcus and B. Typhosus, *J. Infect. Dis.* 42: 149, 1928.
21. Fulton, M. N., and Levine, S. A.: Subacute Bacterial Endocarditis With Special Reference to the Valvular Lesions and Previous History, *Am. J. M. Sc.* 183: 60, 1932.
22. Davis, D., and Weiss, S.: The Relation of Subacute and Acute Bacterial Endocarditis to Rheumatic Endocarditis, *New England J. Med.* 208: 619, 1933.
23. Saphir, O., and Scott, R. W.: The Involvement of the Aortic Valve in Syphilitic Aortitis, *Am. J. Path.* 3: 527, 1927.
24. Libman, E.: Personal communication.
25. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke, *Beitr. z. path. Anat. u. z. allg. Path.* 83: 183, 1930.
26. Clawson, B. J.: Experimental Subcutaneous Rheumatic Nodules, *Am. J. Path.* 4: 565, 1928.

RHEUMATIC HEART DISEASE

III. EMBOLIC MANIFESTATIONS*†

SOMA WEISS, M.D., AND DAVID DAVIS, M.D.
BOSTON, MASS.

THERE has arisen in recent years a keen interest in the study of the nature of vascular occlusions and in the management of patients with this type of vascular lesion. Considerable investigative work has been done, particularly on coronary thrombosis, thrombophlebitis, and pulmonary embolism. On the continent, especially in Germany, suggestive statistics have been gathered indicating a significant rise in the incidence of vascular thrombosis and embolism during the past two decades. No satisfactory explanation of this occurrence has as yet been found.

It is recognized that in the total incidence of vascular thrombosis and embolism, chronic cardiovascular disease plays a prominent rôle. The significance of arteriosclerosis with lesions of the intima, and of cardiac decompensation with slow blood flow, in the development of coronary, cerebral, and visceral arterial thrombosis, is fairly well established. With regard to embolic manifestations, however, the problem is more obscure. A search of the literature reveals that previous studies have centered mainly on the problems of postoperative and postpartum pulmonary embolism. Information as to the relative rôles of various types of heart disease in the incidence of embolic manifestations is not available; and although clinical experience suggests that among patients with "medical" diseases who develop embolism, rheumatic heart disease is frequently present, no reports exist, so far as we know, dealing with this problem statistically. This presentation aims, therefore, to shed some light on the rôle and the clinical nature of embolic manifestations in patients with rheumatic heart disease. The problem contains several practical as well as theoretical aspects.

The basis of the present investigation is a combined analysis of the clinical and the post-mortem data of 5,215 consecutive autopsies performed in the Boston City Hospital during a twenty-five-year period, ending with 1929. Such a combined consideration of clinical and laboratory findings, with the morphological changes observed post mortem, is essential in establishing the relationship between the occurrence of rheumatic heart disease and the *degree* of disability as seen in the

*Read before the American Heart Association, Milwaukee, Wisconsin, on June 13, 1933.

†From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

clinic. Thus, although the total number of cases of rheumatic endocarditis was as high as 474, an incidence of 9.1 per cent, in only 164 instances was the cardiac damage directly responsible for death.^{1, 2} These 164 cases, representing on the whole the most advanced type of rheumatic cardiac damage, were then analyzed as to the presence or absence of embolism and thrombosis. Obviously a differentiation between thrombosis and embolism, even when post-mortem examination is available, cannot always be made with certainty. The clinical manifestations of the onset, the presence or absence of endocardial thrombi, and the character of the occluding plug often, but not always, help in this differentiation.

FREQUENCY AND DISTRIBUTION OF INFARCTIONS

As the absolute differentiation of vascular embolism and thrombosis is not always possible, although in the majority of instances the combined clinical and post-mortem data indicated embolus as the cause of infarct, we shall present embolic manifestations as infarcts. Visceral or pulmonary infarction, single or multiple, involving one or more organs was found in 73 patients (45 per cent). In 1 additional patient thrombosis of the femoral vein was present, and in 11 additional patients extensive ante-mortem auricular thrombi were present without embolic manifestations. This estimation of infarction during the course of rheumatic heart disease must be considered conservative for the following reasons: (1) Emboli may have occurred in the past without leading to infarct or the infarct may have completely healed; (2) some emboli in the skin and in the extremities, which organs were not examined with sufficient thoroughness post mortem, were in all probability overlooked; and (3) owing to the fact that permission to examine the brain was not always obtained, cerebral embolism may have been overlooked in some instances.

TABLE I
DISTRIBUTION OF SITES OF INFARCTION
Patients With Infarcts in One Organ

	NO. OF CASES
Lungs	16
Brain	9
Kidneys	7
Spleen	5
Arteries of legs	2
Mesenteric artery	1
Aorta and iliac arteries	1
Total No. of Cases	41

Single or multiple infarction of one organ was present in 41 patients (Table I); in 22 instances single or multiple infarcts involved two organs (Table II); and in 10 patients infarcts were present in three or

more organs (Table III). The organs involved, in the order of frequency, were: lungs 31, brain 28, kidneys 25, spleen 18, extremities (aortic, iliac, and femoral arteries) 10, intestines (mesenteric artery) 5, and liver 1.

In 4 of the 16 patients with infarets confined to the lungs, mural thrombi of the right auricle were the source of the embolus, and in two instances venous thrombosis was the source. One patient showed a large thrombus in a branch of the pulmonary artery. Thus the source of the embolus could be explained in only 6 of the 16 cases. In the

TABLE II
DISTRIBUTION OF SITES OF INFARCTION
Patients With Infarets in Two Organs

	NO. OF CASES
Lungs and spleen	4
Lungs and kidneys	4
Brain and lungs	3
Brain and kidneys	3
Brain and spleen	2
Kidneys and spleen	2
Kidneys and iliac arteries	1
Lungs and femoral artery	1
Brain and liver	1
Brain and mesenteric artery	1
Total No. of Cases	22

TABLE III
DISTRIBUTION OF SITES OF INFARCTION
Patients With Infarets in Three or More Organs

	NO. OF CASES
Brain, kidneys, and spleen	3
Brain, mesenteric artery, and arteries of leg	1
Brain, lungs, and spleen	1
Brain, kidneys, and aorta	1
Brain, kidneys, and iliac artery	1
Brain, lungs, kidneys, and intestines	1
Brain, lungs, kidneys, and arteries of leg	1
Kidneys, spleen, mesenteric, iliac, and femoral arteries	1
Total No. of Cases	10

group of 15 patients with combined lung and organ infarets a source of the embolus was revealed in 9. Thus, in 6 of this latter group and in 10 of the former group, or in approximately half of the cases, no obvious source of emboli has been found. In 5 instances of the unexplained group of 16, however, there was an acute vegetative process over the tricuspid valve. Pulmonary infarction is sometimes attributed to local thrombosis of the pulmonary vessels as a result of slow pulmonary circulation. This condition instead of embolism may well have been a factor in these cases. The finding of plausible embolic sources of the infarets in about 50 per cent of the cases, however, places the

burden of proof on those who maintain that in these instances the infarcts were caused by local circulatory factors.

Cerebral infarction was the cause of death in 22 cases of the present series, and in one additional case it was regarded as a contributing cause of death. In the 10 cases in which post-mortem examination of the brain was made, cerebromalacia or cysts were found. The cerebral lesions were localized in the internal capsule, the basal ganglia, the restiform body, and the occipital lobe. In every patient with cerebral lesions clinical symptoms were present, and experience with cases not included in this series indicates that the occurrence of cerebral embolism with symptoms and with complete functional recovery and absence of demonstrated infarction is not uncommon. The regularity of clinical manifestation in cerebral embolism is in sharp contrast to the frequent lack of clinical recognition of infarcts of the spleen, kidneys, and other organs.

THE RÔLE OF THE EMBOLIC FACTOR IN THE CAUSATION OF DEATH

The estimation of the rôle of embolism or infarction in the causation of death was often difficult because of the simultaneous presence of other bodily derangements. For this reason the embolic manifestation was held responsible for death only when the clinical condition of the patient took a sharply defined downhill course following the vascular accident.

It is well appreciated that complete recovery, or partial clinical recovery with life of years' duration, following an embolus is not a rare occurrence. Thus, in the present series the combined clinical and post-mortem studies indicated that in at least 11 patients infarcts occurred at some time in the past course of the illness. In 1 patient, a man fifty-five years of age, complete hemiplegia due to embolism developed as long as fourteen years before his last entrance into the hospital. In another case, a female patient thirty-five years of age, embolism in the right femoral artery necessitating amputation of that leg developed while she was in the hospital three and a half years before the fatal cerebral embolism.

TABLE IV

ROLE OF EMBOLISM IN 164 DEATHS FROM RHEUMATIC HEART DISEASE

	NO. OF CASES	PER CENT
Causing death	26	16
Contributing to death	8	5
Probably contributing to death	10	6
Not contributing to death	29	18

Table IV presents a conservative estimate of the frequency of death due to embolism in the 164 cases of fatal rheumatic heart disease. Accordingly in 26 instances, or 16 per cent, death was caused by embolism;

in an additional 8 cases, or 5 per cent, the embolic accident definitely contributed to the occurrence of death. In 10 cases, or 6 per cent, there was suggestive but not conclusive evidence of the contributory influence of embolism. In 17 of the 26 instances of fatal embolism, the accident occurred in patients with slight or no evidence of circulatory failure up to the time of infarction; in the remaining 9 patients there existed a considerable degree of circulatory insufficiency. In this series of 164 cases, as well as in other instances, following the occurrence of embolism, particularly in the brain, lungs, and extremities, the existing circulatory impairment often became intensified, and at times circulatory insufficiency developed in patients with hitherto efficient circulation.

The brain was by far the most frequent site of fatal emboli. In only one instance was embolism of a large branch of the pulmonary artery definitely the cause of death. In 11 other instances pulmonary infarction played an important contributing part, and in 7 cases it played a suggestive rôle. The relation of the pulmonary infarcts to pneumonic processes was often not sufficiently clear to indicate the rôle of the infarcts in the pathogenesis of the pneumonia. Our analysis indicates that in 34 cases of fatal rheumatic heart disease, or 21 per cent, embolism played a chief or contributing part in the death of the patient.

AURICULAR FIBRILLATION AND EMBOLIC MANIFESTATIONS

The cardiac rhythm was determined in 131 of the series of 164 cases. Persistent or paroxysmal auricular fibrillation or flutter was present in 74 patients, or 57 per cent. In a group of 28 patients with extensive auricular thrombi the rhythm was determined in 25, and of this number 22, or 88 per cent, exhibited auricular fibrillation. This high incidence of fibrillation suggests a relationship between auricular fibrillation and the formation of mural thrombi. This is not unexpected, in view of the dilated left auricle which fails to contract.

THE RELATION OF MURAL THROMBI TO THE STATE OF RHEUMATIC ACTIVITY

Auricular endocarditis in addition to valvular endocarditis occurred in a large number of cases in the series. The question was therefore raised as to whether active carditis plays a rôle in the formation of mural thrombi. Rheumatic activity of the heart was determined by the presence alone or in combination of recent rheumatic arthritis, chorea, acute valvulitis, the presence of Aschoff bodies, and the presence of acute pericarditis not otherwise explained. The combined clinical and post-mortem study revealed an activity during the last admission or post-mortem in 70 cases, or 43 per cent; recent activity in 7; and suggestive evidence of activity in 13. In 74 patients activity was not

present. Among the 28 patients with auricular thrombi, activity was definitely present in 5; in 1 patient there was suggestive evidence of activity. Thus activity was present in but 18 per cent as contrasted with 47 per cent of the entire series. Activity is therefore not a factor of primary importance in the formation of mural auricular thrombi in the course of rheumatic heart disease.

SOURCES OF EMBOLI

Definite sources of emboli were found in only 30 of the 73 patients with infarcts. This number includes only those instances of mural thrombi which exhibited definite organization and firm attachment to the wall. In 7 patients with vegetative processes over the valves, the thrombus was prominent. There were a number of instances in which small verrucous vegetations were present over the valves, but the evidence that these vegetations were the source of emboli was insufficient. As the clinical history in the patients without determined source of emboli frequently indicated embolism rather than thrombosis, the explanation of the failure to find the source of the emboli must lie in one of two possibilities: (1) Either the local cardiac thrombi corresponded to the infarct and the source was completely dislodged; or (2) the small verrucous vegetation observed may have been the cause of embolic manifestations.

CLINICAL CONSIDERATIONS

It is evident from the data presented that embolic episodes and infarction occur frequently during the course of rheumatic heart disease, and that these accidents represent a significant rôle in the incidence of death. As observations of patients indicate that purpuric skin lesions or petechiae may also occur in rheumatic heart disease, it follows that embolic manifestations and purpuric spots alone or in combination do not necessarily indicate subacute or acute bacterial endocarditis. Statistically the association of these manifestations with regular cardiac rhythm favors the diagnosis of subacute or acute bacterial endocarditis, and their association with auricular fibrillation the diagnosis of rheumatic endocarditis.

In order to estimate the comparative frequency of peripheral arterial embolic manifestations due to rheumatic heart disease and of embolism caused by other diseases, the underlying etiology of 48 consecutive cases of cerebral embolism occurring in medical wards was determined. The diagnosis was considered definite clinically in every case of the group. Cerebral embolism has been chosen for comparison because, as was shown above, embolism of the brain regularly produces clinical syndrome. In this group of 48 cases, rheumatic heart disease was considered as the source of embolism in 23 instances, chronic myocardial degeneration caused by arterial hypertension or arteriosclerosis in 11 instances, sub-

acute bacterial endocarditis in 9, auricular fibrillation of undetermined etiology in 2, and other causes in 3 instances. Thus, rheumatic heart disease was responsible for the occurrence of embolism more often than any of the other diseases.

There are a few additional bedside observations to which we should like to call attention. 1. It is stated that in visceral embolism the onset of symptoms, and particularly of pain, is sudden. A careful analysis of the patient's sensation reveals, on the other hand, that in splenic and kidney infarcts particularly, the pain often starts as a mild discomfort which slowly or rapidly, in the course of minutes or hours, increases to severe pain. In view of the fact that these organs themselves are not sensitive to pain, but it is their capsule or peritoneal covering which induces pain reflexly, it seems probable to us that in the origin of pain secondary fibrinous perivisceritis plays the important rôle.

2. Because emboli lodged in the larger vessels, particularly in the lower portion of the aorta and the subclavian, radial, brachial, iliac, femoral, popliteal, tibial arteries, can be removed with relative ease and safety provided the diagnosis is made promptly, knowledge of the variations in the clinical picture of embolism along the vessels is important. In addition to the recognition of embolic manifestations of the extremities with classic clinical picture, it is important to appreciate that embolism is not always associated with excruciating pain over the extremities, but coldness, tingling, or numbness may be the only subjective sensation. These mild complaints in patients with heart disease, and particularly with auricular fibrillation, should lead us to careful examination.

3. The result of surgical removal of emboli, as is known, is good if the diagnosis is made within five hours of onset, and fair up to fifteen hours. At times no reliable history exists as to the onset. In 3 cases in which the onset of embolism could not be determined, the patients exhibited marked tenderness on pressure along the arteries below the site of the embolus, and exploration revealed a secondary arterial thrombosis with hemorrhagic inflammatory reaction of the adventitia of the arteries. In these cases surgical interference was of no help. This sign, if confirmed on a larger number of cases, may be a guide in determining contraindication against surgical interference.

Embolism of the arteries of the extremities does not always result in gangrene, and hence in some instances conservative management through establishment of efficient collateral circulation is followed by complete or partial recovery. The decision between conservative care and embolectomy is a difficult and a delicate one. Partial occlusion of the artery, mild symptoms and signs of ischemia below the site of occlusion, good cardiac function, an elapse of a relatively long period after the onset, and occluded artery with good supply of collateral branches favor,

on the whole, conservative management. Any evidence of greatly inadequate blood supply below the site of occlusion calls for prompt surgical interference.

SUMMARY

1. Infarction of one or more organs occurred in 73 cases, an incidence of 45 per cent, of a group of 164 cases in which death was caused by rheumatic heart disease. In 41 instances one organ, in 22 instances two organs, and in 10 instances three or more organs were involved by single or multiple infarcts. The organs involved in order of frequency were: lungs 31, brain 28, kidneys 25, spleen 18, extremities 10, intestines 5, and liver 1.

2. A conservative estimate revealed that in 34 cases, or 21 per cent of the total group, embolism played a chief or contributing part in the death of the patients. Embolism plays, therefore, a significant rôle in the causation of death in rheumatic heart disease.

3. A statistical consideration suggests that auricular fibrillation rather than active rheumatic endocarditis of the auricles plays the primary etiological rôle in the formation of auricular thrombi.


4. Rheumatic heart disease, more than any other type of heart disease, is responsible for embolic manifestations.

5. Clinical considerations bearing on embolic manifestations are discussed.

(For discussion see p. 114.)

REFERENCES

1. Davis, David, and Weiss, Soma: Rheumatic Heart Disease: I. Incidence and Rôle in the Causation of Death. A Study of 5215 Consecutive Necropsies, *AM. HEART J.* 7: 146, 1931.
2. Davis, David, and Weiss, Soma: Rheumatic Heart Disease: II. Incidence and Distribution of the Age of Death, *AM. HEART J.* 8: 182, 1932.



MITRAL STENOSIS*

A CLINICAL AND PATHOLOGICAL STUDY OF ONE HUNDRED CASES*

C. S. STONE, M.D., AND H. S. FEIL, M.D.

CLEVELAND, OHIO

ALTHOUGH correlation of clinical data and pathological findings in cases of mitral stenosis has been repeatedly done^{1, 2, 3, 4, 5} in the light of present-day concepts of heart disease, it is important to reexamine the facts. The anatomical features were studied by Morgagni in 1762, but the clinical features were not adequately recognized until the reports of Bouillaud in 1835,⁶ and it is to him that we are indebted for much of the modern clinical knowledge of this valve lesion. Bouillaud emphasized the frequency of the association of endocarditis and pericarditis with myocarditis. He said: "I have never met a case of carditis [myocarditis as we know it] which was not complicated with endocarditis or pericarditis, and I must admit that the symptoms of these last two inflammatory conditions took my entire attention." Bouillaud also observed the relation of endocarditis to the valvular lesion and its recurrence in cases in which such lesions have once developed.

During the period 1920-1933 100 cases of advanced mitral stenosis came to autopsy at the Cleveland City Hospital, the majority of which had been seen clinically by one of us. The cases of mitral stenosis in a total of six thousand autopsies were distributed evenly over these years. By advanced mitral stenosis we imply the typical fish-mouth or buttonhole deformity of the valve, and we have not included cases showing slight or early pathological evidence of mitral stenosis. These 100 autopsied cases, 70 of which were reviewed in 1931,⁷ form the basis of this report.

CLINICAL FEATURES

Rheumatic Fever.—Of the 90 cases in which a careful history could be obtained there was a history of multiple migratory arthritis in 51 cases (56.6 per cent). Thirty-four patients (66.6 per cent) had but one attack; 13 patients (25.3 per cent) had two attacks; 3 patients (6 per cent) had three attacks; and 1 patient had four attacks. Seven patients (7.7 per cent) gave a history of chorea. A history of scarlet fever was obtained in 3 cases; frequent sore throats were recorded in 10 cases.

*From the Medical Clinic of Western Reserve University at City Hospital.
Read before the American Heart Association, Milwaukee, Wis., June 13, 1933.

Fever.—A temperature above 38° C. was recorded many times during the fatal illness of these patients, and an effort was made to correlate this clinical finding with active cardiac infection. No conclusion could be drawn, as fever was frequently present without pathological evidence of active infection in the heart.

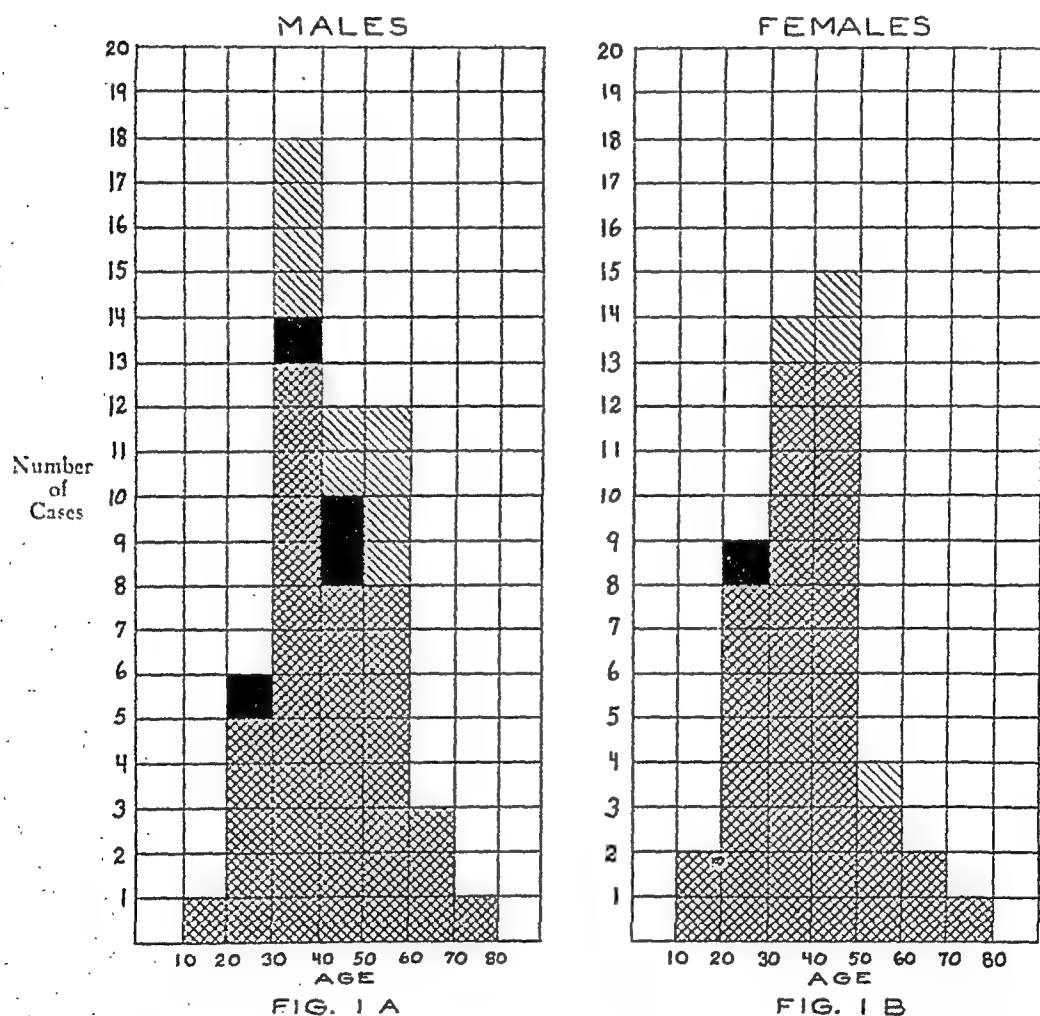
Cerebral Accidents occurred in 12 instances. In 2 of these patients subacute bacterial endocarditis was present; in one patient there was a *Staphylococcus albus* septicemia and a frontal lobe abscess with acute vegetations on the mitral and aortic valves. In one patient (aged thirty-six years) there was a basilar hemorrhage without evidence of arteriosclerosis (or hypertension) or syphilis. In 2 patients there was a history of hemiplegia four years and eight years, respectively, prior to admission to the hospital. In one patient there was a history of hemiplegia on three occasions prior to the last admission (with residual left sided paresis). One patient gave a history of facial paralysis, but the brain was not examined post mortem and the nature of the lesion could not be determined.

Sex and Age.—There were 53 males and 47 females, although the ratio of male to female patients on the medical service was as 3:2, substantiating previous reports concerning the higher percentage of mitral stenosis in females. The sex and age distributions are illustrated in Fig. 1-A and B, in which all of the cases are tabulated. In Fig. 1-A are tabulated the male cases while in Fig. 1-B are tabulated the female cases. The age distribution is much the same in the two graphs, although the male patients past fifty years of age outnumbered the female patients (M 16, F 7). The average age of death of all of the patients was forty and six-tenths years; the average age of the males was forty-two and seven-tenths years, and the average age of the females was thirty-eight and six-tenths years. These figures agree with those reported by previous writers.

Race.—There were 9 negro patients: 3 males and 6 females. This total percentage of 9 per cent may be compared with the negro population of the medical service of City Hospital which is 20-30 per cent of the total. Davis and Weiss report 3.8 per cent negroes in their 474 rheumatic heart deaths as compared to 8 per cent negroes of the total autopsy series. Whether this apparent lower percentage of rheumatic heart disease in colored patients is due to migration (as suggested by Davis and Weiss) or whether the incidence is actually lower cannot be determined definitely.

In studying Fig. 1, 72 patients or 72 per cent died between the ages of twenty and fifty, the largest number dying in the fourth decade (32 per cent). The sexes shared nearly equally in the mortality between the ages of twenty and fifty. It is seen that in the majority of our cases death occurred before the age of fifty. The 5 cases of

subacute bacterial endocarditis are seen in the diagram as solid black blocks and all occurred before the age of fifty years. The series of Davis and Weiss^{8, 9} comprising 474 autopsied cases of rheumatic heart disease showed that 164 cases (34.5 per cent) of the total group died directly as the result of rheumatic heart disease, whereas in our 100 cases of mitral stenosis 81 or 81 per cent died directly as the result of rheumatic heart disease (heart failure). If the case of acute and the 5 cases of subacute bacterial endocarditis are included, this figure



risers to 87. When the noncardiac deaths are subtracted from the series (the lighter areas at the top of the columns of Fig 1, A and B), it is seen that the predominance of deaths up to the age of fifty is still present.

Effect of Pregnancy on the Length of Life.—Recent clinical studies have lessened the fears of clinicians in dealing with pregnancy in mitral stenosis.^{10, 11, 12, 13} Our cases emphasize the small part pregnancy plays in bringing on failure or as a cause of death. In the 47 female patients in this series there were 5 who were unmarried. In 10 cases there were no children and in 7 cases our history was uncertain. The remaining women (25) bore children as seen in Table I.

The average age of these 25 women who bore children was thirty-nine and four-tenths years. The average age of the women who did not bear children was forty-one years (excluding from this figure two children aged thirteen years and fourteen years). The average age

TABLE I

NO. OF CHILDREN	NO. OF PATIENTS
1	8
2	6
3	2
4	1
5	0
6	2
7	4
8	1
9	0
10	0
11	0
12	0
13	1

of all the females was thirty-eight and six-tenths years and the average age of all the males was forty-two and seven-tenths years. These figures suggest that the life span is only slightly reduced in women who bear children. A careful study of our cases reveals a number of instances in which there may have been some influence exerted by pregnancy.

CASE 9.—One child (cesarean) two years before death; died of bronchopneumonia.

CASE 21.—Died two weeks after delivery (failure). First pregnancy.

CASE 42.—Abortion at sixth month of pregnancy.

CASE 52.—Had failure after childbirth, fourteen months before death. Second child.

CASE 63.—Heart trouble at fourteen; six children and four miscarriages. Died at age of forty years of streptococcus septicemia following induced abortion.

CASE 95.—Died two weeks after birth of second child; had failure all through pregnancy.

The following case emphasizes the fact that multiple pregnancies may not apparently affect the life span of the patient.

CASE 13.—Had thirteen children, last one born at age of forty-one; failure at forty-three, died at forty-eight.

There appears to be a definitely deleterious effect of pregnancy in women with mitral stenosis when failure or marked reduction in exercise tolerance antedates pregnancy. That the great majority of rheumatic hearts bear pregnancy well seems evident. This view is shared by Daly,¹⁰ Reid,¹¹ and Hamilton and Kellogg.¹²

Auricular Fibrillation.—In 94 cases the mechanism was accurately, and in most instances electrocardiographically, studied. Auricular fibrillation was present in 50 cases or 53.1 per cent. Normal mechanism was present in 43 cases and heart-block in one case. In 52 cases

pulmonary infarcts were found post mortem of which 46 cases were carefully studied as to mechanism. Thirty of these or 65 per cent had auricular fibrillation. Intracardiac thrombi were frequently associated with auricular fibrillation (22 out of 37 cases). In none of the 5 cases of subacute bacterial endocarditis did auricular fibrillation occur.

The rarity of auricular fibrillation in subacute bacterial endocarditis has been noted by Levine and Fulton.¹⁴ Likewise, Rothschild, Sacks, and Libman¹⁵ observed that auricular fibrillation was unusual in subacute bacterial endocarditis, finding but one case in 109 patients in the active or bacterial phase of the disease, and in 3 patients among 14 cases in the bacteria-free or healed stage. The rarity of auricular fibrillation in subacute bacterial endocarditis¹⁵ may be explained in part by the rarity of subacute bacterial endocarditis in advanced mitral stenosis. Auricular fibrillation is definitely more common in mitral stenosis, especially in advanced cases.

Blood Pressure.—Boas and Fineberg¹⁶ and Levine and Fulton¹⁷ have recently reemphasized the relationship between mitral stenosis and hypertension. In 7 cases hypertension was observed, but in view of the late stage of many of our hospital admissions this figure is doubtless too low to be compared with the clinical observations of the other investigators.

Incidence of Tuberculosis.—Rokitansky,¹⁸ in 1846, wrote that heart disease accompanied by chronic passive congestion of the lungs excluded pulmonary tuberculosis. Tileston,¹⁹ in 1908, reviewed the conflicting literature and reported a series of 128 autopsied cases of mitral stenosis which showed a much lower percentage of pulmonary tuberculosis than the material from which they were drawn. The greater the stenosis the less was the incidence of tuberculosis and the patients with a high degree of stenosis were free from active tuberculosis. Tileston believed that pulmonary tuberculosis is less likely to occur in mitral stenosis, and if present runs a milder course and tends to heal. This he believed was due to the chronic pulmonary congestion. Three of our patients had chronic fibroid tuberculosis and one additional patient had tuberculous mesenteric lymph nodes.

Causes for Hospitalization and Duration of Failure.—Eighty-one cases or 81 per cent were admitted to the hospital because of congestive failure of varying degree. The duration of the failure from the onset of symptoms to death varied greatly and averaged three and a half years.

Subacute Bacterial Endocarditis.—The importance of this superimposed infection as a cause of death from heart disease may be judged from the figures of Davis and Weiss⁹ who reported finding 47 cases of subacute bacterial endocarditis in a total of 474 necropsies

of rheumatic heart disease (9.9 per cent). In the 269 cases in which death was attributable to cardiac disease this number, 47, represents a percentage of 17.4 per cent. Subacute bacterial endocarditis occurred in 5 cases of our series. In 88 cases of our series death could be directly attributable to heart disease either due to infection or to failure. In this group there were 5 cases of subacute bacterial endocarditis (5.6 per cent). During the period covered by our studies there were 40 autopsied cases of subacute bacterial endocarditis, so the percentage of mitral stenosis in this small series was 12.5 per cent. These facts substantiate the findings of Fulton and Levine¹⁷ and of Sprague.²⁰ The latter author found mitral stenosis 5 times in a series of 20 cases of subacute bacterial endocarditis (25 per cent) which were not autopsied. The calcified and comparatively avascular scar may be responsible for this infrequency. The immobility of the mitral valve in advanced stenosis and the consequent absence of trauma to the valve during systole has also been suggested as a cause of the infrequent association of these two conditions. Of interest was the finding of combined rheumatic valve lesions in all 5 of our subacute cases and in all but one the mitral valve was seriously involved with the superimposed infection. In this one case with slight rheumatic scarring of the aortic valve, the lesions were almost exclusively limited to this valve.

Acute Bacterial Endocarditis likewise was uncommon and occurred in only two instances. One patient had septicemia due to *Staphylococcus albus* and died of a cerebral hemorrhage (male, white, aged thirty-three years). Another patient had septicemia following an abortion. There were 13 cases of acute bacterial endocarditis autopsied during the period covered by these observations, the majority of which were due to pneumococcus endocarditis in pneumonia.

Causes of Death.—Eighty-one patients or 81 per cent died directly as the result of cardiac disability attributable to the rheumatic heart disease. In addition, 5 or 5 per cent died of subacute bacterial endocarditis. Besides congestive failure and acute and subacute bacterial endocarditis, there were indirect causes of death as the result of heart disease, the cases with embolism and with infarction with varying degrees of failure.

Heart Weights.—Table III shows the heart weights in summary. Examination of Table III reveals a great variation in the heart weights, although the average weight of the hearts with combined lesions tends to be greater. The wide range of weights makes it difficult to draw any conclusions concerning the influence of the associated valve lesions.

TABLE II
SUMMARY OF PATHOLOGICAL FINDINGS

THE PATHOLOGICAL FINDINGS IN THE CARDIAC DEATHS	
Failure alone	68 or 68%
Failure associated with:	13 or 13%
Coronary sclerosis and occlusion	1%
Bronchopneumonia	5%
Pulmonary embolism	1%
Large pulmonary infarct	1%
Cerebral hemorrhage	1%
Erysipelas	1%
Acute salpingitis	1%
Uremia and hydronephrosis due to carcinoma of cervix	1%
Encephalomalacia	1%

PATIENTS DYING OF PRIMARY CAUSES OTHER THAN CARDIAC FAILURE.

Subacute bacterial endocarditis—with no failure	3
with slight failure	2
Encephalomalacia and bronchopneumonia	2
Acute bacterial endocarditis and cerebral hemorrhage (<i>Staphylococcus albus</i>)	1
Arteriolar disease with hypertension with bronchopneumonia and heart-block	1
Carcinoma head of pancreas and encephalomalacia	1
Erysipelas with septicemia (<i>Streptococcus hemolyticus</i>)	1
Bronchopenumonia and pyonephrosis	1
Bronchopneumonia	2
Lobar pneumonia	1
Carcinoma of stomach	1
Pernicious anemia with bronchopneumonia	1
Septicemia following abortion	1
Purpura hemorrhagica	1

Tricuspid Valvulitis (varying degrees of stenosis).—When mitral stenosis was associated with aortic stenosis, the tricuspid valve was involved in 12 per cent of the cases, while mitral stenosis was associated with tricuspid stenosis alone in only 5 per cent of our series. This is in agreement with the published series of Dressler and Fischer²¹ who found mitral, aortic, and tricuspid stenosis present in 11 instances in a series of 120 cases of valvular heart disease (9.1 per cent).

Associated Valve Lesions (without stenosis).—The aortic valve was scarred in 20 per cent; the tricuspid valve in 15 per cent, and the pulmonic valve in 2 per cent.

TABLE III

	%	AVERAGE WT. IN GM.	RANGE OF WT. IN GM.
Mitral stenosis alone	54	462.7	250-700
Mitral stenosis with aortic stenosis	29	530.0	250-925
Mitral stenosis with aortic and tricuspid stenosis	12	545.8	300-750
Mitral stenosis with tricuspid stenosis	5	470.0	425-525

Pericarditis.—Chronic adhesive pericarditis was found in 10 per cent of the cases and acute pericarditis in 1 per cent.

Acute Verrucose Endocarditis.—In substantiating the original findings of Bouillaud, we observed acute verrucose endocarditis in 48 per cent of our cases. This agrees with the clinical observations of Cutler, Levine and Beck.²² Acute vegetations were found on the mitral valve in 42 per cent; on the aortic in 29 per cent; on the tricuspid in 9 per cent; and on the pulmonic valve in 2 per cent.

Intracardiac Thrombi were found in 37 cases as seen in Table IV. Thrombi and infarction were more common in the presence of acute verrucose endocarditis.

TABLE IV

Right ventricle	4	10.8% of 37 cases
Left ventricle	2	5.4% of 37 cases
Right auricle	16	43.2% of 37 cases
Left auricle	19	51.3% of 37 cases

The cardiac mechanism was studied in these 37 cases, in 34 of which the data were reliable. Table V is a tabulation of the findings.

TABLE V

Auricular fibrillation	22	64.7%
Normal sinus rhythm	12	35.3%
No record	3	8.1%

Infarction of various viscera was present in 52 cases and the distribution is seen in Table VI, together with cardiac mechanism.

TABLE VI

		MECHANISM		PER CENT
Pulmonary	33	Auricular fibrillation	30	65.2
Renal	21	Normal sinus rhythm	16	34.9
Splenic	13	Not recorded	6	11.5
Hepatic	1			

No definite relationship could be established between the presence of intracardiac thrombi and visceral infarction.

The incidence of auricular fibrillation in the entire series was 53.1 per cent, in the cases having intracardiac thrombi 64.7 per cent, and in 65.2 per cent of the cases showing infarction of various organs. A definite relationship can be made out between the occurrence of auricular fibrillation and the finding of intracardiac thrombi and of infarction.

Pulmonary Embolism was present in 7 cases. Thrombi were found in various other vessels:

Coronary arteries	2
Subclavian arteries	2
Optic artery	2
Common iliac artery	1
Abdominal aorta	1
Renal artery	1
Portal vein	1

Cholelithiasis.—Broekbank²³ found cholelithiasis in 21.8 per cent of 87 cases of mitral stenosis, while in 1347 post mortems gallstones were present in 7.4 per cent. Gallstones were present in 3 per cent of our cases. There appears to be no relationship between chronic cardiac failure as caused by mitral stenosis and the formation of gallstones.

SUMMARY

In a clinical pathological review of 100 autopsied cases of advanced mitral stenosis the findings of previous investigators have largely been substantiated.

1. A rheumatic history was obtained in 56.6 per cent, and 66.6 per cent of these cases had but one attack.

2. Cerebral accidents occurred in 12 instances.

3. Females and the white race predominated. The average age of death of the males was forty-two and seven-tenths years; of the females thirty-eight and six-tenths years. Pregnancy did not appear to influence greatly the onset of failure, nor did it directly cause death.

4. Auricular fibrillation was present in 53 per cent; intracardiac thrombi and pulmonary infarction were in the majority of the cases associated with auricular fibrillation. In none of the 5 cases of subacute bacterial endocarditis was fibrillation present.

5. Chronic fibroid tuberculosis was found in 3 cases.

6. Eighty-seven patients died as the result of cardiac disability. Eighty-one per cent of the patients died of circulatory failure, and subacute bacterial endocarditis was an uncommon cause of death (5 per cent). Acute bacterial endocarditis occurred once. Acute verrucose endocarditis was present in 48 per cent of the cases.

7. Mitral stenosis was the sole lesion in 54 per cent of the cases. Tricuspid stenosis was more frequently associated in the patients having aortic stenosis.

8. The heart weight tends to increase with multiple valve lesions.

9. Auricular fibrillation was more frequent in the cases with intracardiac thrombi and with infarction of various origins than in the entire series.

10. Cholelithiasis was present in only 3 per cent of the series.

(For discussion see p. 113.)

REFERENCES

1. Phear, A. G.: *Lancet* 2: 716, 1895.
2. Samways, D. W.: *Brit. Med. J.* 1896, p. 1567.
3. Thayer, Wm. S.: *Tr. A. Am. Physicians*, 1911.
4. Cabot, R.: *Trans. A. Am. Physicians*, 1914.
5. Landis, E.: *Diseases of the Chest and the Principles of Physical Diagnosis*, ed. 2, 1920, p. 725.
6. Bouillaud, J.: *Traité clinique des Maladies du Cœur*, ed. 2, Paris, 1841, J. B. Baillière.
7. Einsel, I. H., Feil, H. S., and Stone, C. S.: *Ohio State M. J.* 27: 783, 1931.
8. Davis, D., and Weiss, S.: *AM. HEART J.* 7: 146, 1931.
9. Davis, D., and Weiss, S.: *AM. HEART J.* 8: 182, 1932.
10. Daly, P. A.: *J. A. M. A.* 82: 1439, 1924.
11. Reid, W. D.: *Am. J. Obst. & Gynec.* 19: 63, 1930.
12. Hamilton, B. E., and Kellogg, F. S.: *J. A. M. A.* 91: 1942, 1928.
13. Pardee, H. E. B.: *Am. J. M. Sc.* 164: 847, 1922.
14. Fulton, M. N., and Levine, S. A.: *Am. J. M. Sc.* 183: 60, 1932.
15. Rothschild, M. A., Sacks, B., and Libman, E.: *AM. HEART J.* 2: 356, 1927.
16. Boas, E. P., and Fineberg, M.: *Am. J. M. Sc.* 172: 648, 1926.
17. Levine, S. A., and Fulton, M. N.: *Am. J. M. Sc.* 176: 465, 1928.
18. Rokitansky, C.: *Manual of Pathologic Anatomy*, Swains Translation for the Sydenham Society, London 1: 316, 1854.
19. Tileston, W.: *J. A. M. A.* 50: 1179, 1908 (for full bibliography).
20. Sprague, H. B.: *J. A. M. A.* 94: 1037, 1930.
21. Dressler, W. W., and Fischer, R.: *Klin. Wehnschr.* 8: 1267, 1929.
22. Cutler, E. D., Levine, S. A., and Beck, C. S.: *Arch. Surg.* 9: 689, 1924.
23. Brockbank, E. M.: *Edinburgh M. J.* 4: 51, 1898.

RHEUMATIC HEART DISEASE IN SOUTHERN FLORIDA*

INCIDENCE AND CLINICAL NOTES

E. STERLING NICHOL, M.D.

MIAMI, FLORIDA

THIS paper represents an attempt to present a picture of rheumatic heart disease as it occurs in Southern Florida (Miami), together with a review of the literature bearing on the geographical distribution of rheumatic heart disease. The incidence of the disease has been determined by examination of hospital records, private case records, and through a survey of school children. Although the groups are relatively small, it is hoped that the value of the data is enhanced by the strictly personal nature of the inquiry.

INCIDENCE OF RHEUMATIC FEVER

A previous survey¹ of patients admitted to Jackson Memorial Hospital, Miami, during the years 1925 to 1930 revealed only 4 cases of rheumatic fever and 6 cases of chorea among 31,153 admissions. From 1930 to 1933 there have been only 4 additional cases of rheumatic fever and none of chorea among 16,286 admissions, making a total of 14 cases of rheumatic fever or chorea among 47,439 total admissions. Approximately 13,000 were medical cases, giving an incidence of practically 1 case of rheumatic fever or chorea per thousand medical cases. The hospital admits patients from all walks of life with a number of children included. About one-fifth of the medical admissions were colored patients, but only one instance of rheumatic fever occurred in this race. The ages of the 4 cases since the previous report ranged from eleven to twenty-four years. The cases were mild, monoeyelic in type, with carditis apparent in one only, a woman twenty-four years of age who is the only adult Miamian I have ever known to develop an initial attack of rheumatic fever.

Among approximately 4,200 private patients seen in the office and home by the author during the same eight-year period (1925 to 1933) there have been only 3 cases of rheumatic fever or chorea originating in Miami, and one of these is included in the foregoing hospital group. By combining the two groups a total of 16 cases of rheumatic fever or chorea were encountered among 16,200 medical cases.

Because of some supposed relationship between scarlet fever and rheumatic fever, it should be noted that scarlet fever occurred four times more frequently than rheumatic fever, there being a total of 65 cases during the eight-year period, in the combined series. On the other

*Read before the American Heart Association, Milwaukee, Wisconsin, June 13, 1933.

hand, acute nephritis is just as rare in this area as is rheumatic fever, there being 15 cases in the hospital series and none seen in private work.

RHEUMATIC HEART DISEASE

During the years 1931 and 1932 there were 224 patients with heart disease admitted to the wards of Jackson Memorial Hospital under my supervision. Rheumatic heart disease was the etiological diagnosis in 57 cases, or 25.9 per cent. It might seem that since this figure is not much smaller than that of similar morbidity statistics from northern hospitals that Miami clinicians must be overlooking the rheumatic type of heart disease in its inception, if the incidence of clinical rheumatic fever is so low. But further analysis shows that in the rheumatic group of 57 patients only 2 or 3.3 per cent were natives of southern Florida while 22 or 10 per cent of the entire group claimed the Miami area as their birthplace. In the rheumatic group there were 9 negroes (14 per cent), but there were 64 or 28.5 per cent in the entire group. The ratio of rheumatic heart disease among the 160 white patients was more than double that in the colored, being 30 per cent or 48 cases.

During the same period in a small cardiac clinic conducted by the author, 47 patients with organic heart disease were cared for, and of these 14 or 29.9 per cent had rheumatic heart disease, but only 3 of the rheumatic patients were born in the Miami area.

Among 142 patients with organic heart disease under observation in private work during the past two years, there were 32 or 22.5 per cent with rheumatic heart disease. Only one of this type was a native of southern Florida however, while 10 per cent of the entire group were born in this area.

Combining the three groups of hospital, clinic, and private cases, gives a total of 413 patients with organic heart disease studied during the two-year period, with rheumatism the etiological factor in 103 or 24.9 per cent. Only 6 patients with rheumatic heart disease were natives of southern Florida.

During the same period 42 instances of heart disease were found at autopsy, with 7 hearts showing morphological evidence of rheumatic etiology, giving an incidence of 21.4 per cent. None of the 7 patients had been natives of southern Florida.

School Survey.—Because of the likelihood of mild attacks of rheumatic fever in children being overlooked, thus making the disease appear rarer than it actually is, an examination of elementary school children (Grades I to VI) in the Miami area was made. Fifteen hundred children born in Miami (including children coming to Miami during the first year of life in some cases) and a similar group of children born in northern states were examined by the author in the past year.* (For

*The following physicians kindly cooperated in the examination of some of the school children: Dr. Wm. McKibben, Dr. Donald Gowe, Dr. Dan Hardie, and Dr. Rothwell Lefholz.

practical purposes any child born north of Florida was included in the northern group, but the majority of these children had moved to Miami from above the Mason and Dixon line.) A record was made of all cases of heart disease found during the examinations. In a few instances x-ray and electrocardiographic examinations were used as an aid in establishing the diagnosis in questionable cases, but for the most part reliance was placed on the accepted physical signs of heart disease in children. Undoubtedly some mistakes were made, but since all questionable cases were seen by the same examiner (the author), it is likely that the rate of incidence in the two groups is fairly accurate.

Among the children born in the Miami area there were 7 cases of rheumatic heart disease, only one of which showed marked signs of mitral stenosis. A history of rheumatic fever was obtained in 2 cases only. In the northern group 24 children showed signs of rheumatic heart disease, but 2 of these gave a history of having their first attack of rheumatic fever after moving to Florida. Even making allowance for such an event in other cases, this survey indicates that rheumatic heart disease is found in children born in the Miami area about one-third as frequently as in children who have moved to southern Florida from the North. But in view of the extremely low incidence of clinical rheumatic fever in the Miami area, it is surprising to find even 7 cases (an incidence of 0.46 per cent) of rheumatic heart disease among Miami born children. Very likely the insidious invasion of the heart is undetected in its active state by parents and physicians alike.

In passing it should be noted that among the 3,000 children there were 84 instances of systolic murmur classified as functional, about equally divided between the two groups. Of course some of these murmurs, notably the apical systolic murmurs, may eventually prove to be due to rheumatic heart disease. There were 4 cases diagnosed as congenital heart disease. Further analysis of the findings in these children would have no bearing on the present theme.

CLINICAL OBSERVATIONS

Two transportation experiments with patients with rheumatic fever have been carried out since 1929. The first, by Coburn,³ is described in detail in his monograph, and consisted of sending a group of 10 children with rheumatic heart disease, characterized by tenacious activity, from New York to Puerto Rico, to observe the benefits to be obtained by a change of climate. The results were, to quote Coburn briefly, that "the rheumatic process subsided during three months in the Tropics, disappeared clinically during six months in the Tropics, and evidenced itself with sudden reappearance of symptoms in some instances shortly after the return of the patients to New York."

A similar transportation experiment has been in process in the past three winters at Miami Beach under the auspices of T. D. Jones,⁴ of

Boston, and C. F. Roche, of Miami Beach. These workers recently related their results, confirming Coburn's good report. Fourteen children with active rheumatic heart disease were sent down from Boston for observation under hospital-solarium management. Two children eventually succumbed, but the others made marked improvement, with gain in weight and loss of clinical symptoms at a rapid pace as the striking features of the experiment. Most of these patients retained their improved state after their return to Boston.

During the past five winter seasons in Miami I have had the opportunity to watch the clinical course of 14 children or young adults with rheumatic heart disease sent down from the North by their physicians. Though a few patients were fairly sick on their arrival, the majority had only slight daily fever or were free of fever before leaving the North, rheumatic activity being indicated only by mild joint symptoms, residual tachycardia, or laboratory findings. Two of this group died, one being a girl of eighteen who suffered attacks of pulmonary edema after coming to Miami and died in a similar attack shortly after returning to New York in the late spring. The other death occurred in a young woman, twenty-one years of age, who remained in Miami two years and had improved enough to undertake light clerical work for nearly a year, only to have a recrudescence of her rheumatic carditis following a "cold," terminating in congestive heart failure and death. Morphological examination of the heart revealed a rheumatic endocarditis involving the mitral and aortic valves, and rheumatic lesions in the myocardium.

A third patient, a Greek girl of seventeen years, apparently developed subacute bacterial endocarditis. She returned North recently, against advice, having stayed in Miami about three months, with some clinical improvement evident the first few weeks.

All of the other patients improved decidedly while in Miami, losing in a few weeks' time, with two exceptions, clinical evidence of an active rheumatic lesion. Gain in weight was pronounced in all but 2 children who failed to eat properly, but even these 2 patients made good progress otherwise. In each instance unless definite fever existed, daily sun baths were instituted routinely. Improvement first showed up by the changed spirit and appearance of the patients. Having had the opportunity of seeing similar cases retain their activity and ill-health over long periods of time when residing in the North, I have been greatly impressed with the giant strides toward normal health taken by the patients in this little group.

One particular patient warrants further comment, owing to the severity of his initial infection. He was the ten-year-old son of a physician in Tennessee. In July of last year he was seized with severe, one might say fulminating, rheumatic fever, with all the classical signs including many rheumatic nodules. A blood culture yielded a growth of

6 2194

Streptococcus viridans. After three months his symptoms had subsided enough to permit his traveling to Miami. On arrival, a low grade fever and mild joint symptoms persisted, and examination revealed mitral stenosis, cardiac enlargement, anemia, a poor nutrition state, a rapid pulse, and a palpable spleen. There were no residual nodes, no petechiae, no splintering of the nails, no red blood cells in the urine. The question naturally arose as to whether his infection was of subacute bacterial type, but the history of rheumatic nodules seemed to rule out this possibility. (After the first two blood cultures, subsequent cultures were negative.) Although during the first weeks of his stay in Miami the progress of this patient was slow, as soon as it became possible to put him in the sunshine daily he began to pick up in appetite and spirits, lost his joint symptoms and gained 40 pounds in weight. In fact, the weight gain was so rapid that it became necessary to restrict his diet eventually. In spite of the fact that this patient still shows occasional slight elevation of temperature, with a pulse ranging from 84 to 96, I believe his ultimate recovery is certain, provided he escapes reinfection. It is unlikely, in view of the severity of his infection, that he would have made such fine progress had he remained through the winter and spring in the latitude of Tennessee.

In evaluating the effect of the climatic factor on the course of the disease, it should be borne in mind as recently emphasized by Grace⁵ and others, that most cases of rheumatic fever tend to subside spontaneously without benefit of specific therapy. However, the *rapidity* with which clinical evidence of rheumatic activity in these patients disappears after arriving in southern Florida is convincing evidence that the removal of such patients to a subtropical climate amounts to "specific therapy."

REVIEW OF LITERATURE

The low incidence of rheumatic fever in tropical countries has been commented upon by many physicians during the past fifty years. Probably the first to emphasize this point was Hirsch,⁶ who showed that it was practically absent from tropical countries, except where high plateaus existed. Other early contributions came from Newsholme⁷ and Buchanan,⁸ the latter showing its rarity in Southern India. During the last ten years renewed interest has developed in the effect of geographical location and climate on the occurrence of rheumatic fever and rheumatic heart disease, and some of the published data will be briefly summarized as follows:

Faulkner and White⁹ found by examination of hospital statistics that the incidence of rheumatic fever varied in different localities from 0.2 per cent to 5.8 per cent, with cold, wet climates predisposing to the higher rates. Harrison and Levine¹⁰ concluded from a study of hospital incidence rates that both rheumatic fever and rheumatic heart disease

are more prevalent in northern than in southern cities in the United States. The Seegals¹¹ showed from hospital statistics that even over a period of years the admission rate of rheumatic fever is greater in the northern than in the southern region of this continent. Davis and Weiss¹² studied a large series of autopsy records in Boston, and after correlating the morphological and clinical data, reported an incidence of rheumatic heart disease of 9.1 per cent.

The incidence of rheumatic heart disease among school children has been commonly stated to be approximately 2 per cent in the United States and England. A recent report from England by McSweeney¹³ places the incidence at 1.5 per cent, while surveys of the children in Boston,¹⁴ New York,¹⁵ and Philadelphia¹⁶ showed rates of only 0.66 per cent, 0.89 per cent, and 0.8 per cent, respectively. Naturally the figures vary with the carefulness of the examinations and the inclusiveness of the diagnosis "rheumatic heart disease."

Longcope¹⁷ found the admission rate for rheumatic fever in Johns Hopkins Hospital, Baltimore, was 1.3 per cent, and in commenting on the milder symptoms of the disease in that city as compared to New York, he emphasized the ease of overlooking rheumatic fever in semitropical localities. In several southern states recent surveys have shown a low incidence of rheumatic disease. Stone and Vanzant¹⁸ found a rate of 7.3 per cent among hospitalized patients with heart disease in Galveston, while Schwab and Seulze¹⁹ found a rate of 3.4 per cent among dispensary cardiac patients in the same city. Houston²⁰ found the incidence of rheumatic fever among hospital admissions in New Orleans to be 0.07 per cent. On the other hand, McLean²¹ reported an incidence of rheumatic fever in the Children's Hospital, Birmingham, of 1.8 per cent, with carditis in the majority. He feels that rheumatic heart disease is more common in the South than is generally recognized.

A marked disparity in the incidence of rheumatic fever (including chronic valvular disease and chorea) in different sections of Virginia has quite recently been shown by Wood and Hart.²² These authors found the incidence among total hospital admissions in Piedmont (central Virginia) more than three times that in Tidewater (eastern Virginia), being 0.48 per cent and 0.15 per cent, respectively.

Coffen²³ reported the incidence of rheumatic fever in the Pacific Northwest as 0.1 per cent, although 5 per cent of hospital admissions showed rheumatic heart disease. He believes the discrepancy is explained by the migration of persons with previously damaged hearts into that vicinity. In the Rocky Mountain region, 44 per cent of heart disease is of the rheumatic type, according to Viko.²⁴

The figures from China have not been very enlightening. Meleney and Kellers²⁵ found in Northern China frequent instances of mitral stenosis at autopsy, although rheumatic fever was seldom seen. Ander-

son,²⁶ in Hongkong, found only 5 cases of rheumatic fever or chorea among 3,000 medical admissions to hospitals, yet stated that endocarditis occurred frequently. These discrepancies are probably due to lack of recognition of rheumatic fever in its milder forms, it being rather scantily clad with clinical symptoms. More recently Maxwell²⁷ has stated that rheumatic fever is absent in the south of China, but more often met with in the northern parts.

In 1930, Clark²⁸ again proclaimed the rarity of rheumatic fever and rheumatic heart disease in the tropics, stating that during an experience of 33 years in the Malay States he never saw a case of rheumatic fever or chorea, nor did he encounter among 150,000 hospital patients a single instance of mitral stenosis. In addition, he found at autopsy no hearts bearing "the scarred valves of rheumatic disease."

Coburn's³ monograph in 1931 added considerably to our knowledge of the geographical distribution of rheumatic heart disease. He found Puerto Rico entirely free from clinical rheumatic fever, and is authority for the statement that no gross or microscopic lesions of rheumatic disease were found in nearly 500 autopsies performed by Lambert and Pappenheimer in San Juan, although Koppish encountered 2 cases in necropsy material. Getz, in Panama, is quoted as reporting 5 cases of rheumatic fever in 11,000 hospital admissions yearly, and in addition, finds rare instances of rheumatic carditis at autopsy. By correspondence and direct investigation Coburn gathered data from other countries, showing that the disease is prevalent and severe between latitudes 50 and 40 degrees North diminishing in warmer climates and almost unknown between the Tropics of Cancer and Capricorn, increasing again as cooler climates are reached until it becomes common again between 30 and 40 degrees of latitude South. Thus, in the Eastern Hemisphere it is present in South Africa and Australia, and especially prevalent in Northern Europe, but no tropical place was found in which rheumatic disease is common.

In a report of an investigation for the American Heart Association, Paul²⁹ has recently summed up the findings regarding the regional distribution and climatic influence on rheumatic fever. "Is it possible," he asks, "that in spite of the conflicting data rheumatic fever may exist insidiously without manifest joint symptoms to give away the diagnosis and that certain climates serve to accentuate the joint symptoms and thus give a false idea of the prevalence of the disease?"

COMMENT

The reason for the absence of rheumatic fever in the tropics is not clear. Most authors believe that the low incidence of upper respiratory infections bears a close relationship to the absence of rheumatic fever. Coburn³ showed that epidemic upper respiratory infections with *Streptococcus hemolyticus*, common in New York City, are rare in the tropical

environment of Puerto Rico, and that residents in Puerto Rico have an almost constant pharyngeal flora. He feels that the evidence indicates that this is the basic explanation for the rarity of rheumatic fever in Puerto Rico.

Jones and Roche⁴ also feel that the absence of respiratory infections has a bearing on the improvement noted in their transportation experiment at Miami Beach, but are convinced that the absence of hemolytic streptococcus is not the essential explanation.

In my opinion, one cannot claim an absence of respiratory infections in southern Florida. The common cold in this climate seems nearly as prevalent as elsewhere, though, on the whole, epidemics of colds and "influenza" in Miami seem mild as compared with those of colder climates. Some idea of the comparative incidence of lobar pneumonia and rheumatic fever was obtained by a previous survey¹ which showed 150 cases of lobar pneumonia in the group of 31,153 hospital admissions that contained only 10 cases of rheumatic fever.

In any event, an inquiry into the prevalence of hemolytic streptococcus in the flora of throats in Miami residents would be enlightening.

It is possible that rheumatic fever is absent in tropical climates because of alterations in the physical chemistry of the human organism, due to the climatic factor, thus creating in the person living in the tropics a poor environment for the infective agent, whatever its identity. It is likely that the student of physical chemistry will eventually explain the impressive immunity against the agent of rheumatic fever with which the tropical resident is endowed.

SUMMARY

1. Only 16 cases of rheumatic fever or chorea occurred among 16,200 medical cases in Miami during a period of eight years.

2. Among 413 patients with organic heart disease seen by the author during the past two years in hospital, clinic, or private practice, 103, or practically 25 per cent were of rheumatic etiology. However, in only 6 instances did the rheumatic disease originate in southern Florida.

3. Rheumatic heart disease is found with only one-third the frequency among elementary school children born in Miami that it is found in children born in the North who have taken up residence in Miami.

4. There is evidence that patients with active rheumatic heart disease improve at a more rapid rate if moved to southern Florida from northern climates during the cold months.

(For discussion see p. 117.)

REFERENCES

1. Nichol, E. Sterling: Rheumatic Fever and Lobar Pneumonia: Notes on Occurrence in Southern Florida, *J. Florida M. A.* 17: 366, 1931.
3. Coburn, Alvin F.: *The Factor of Infection in the Rheumatic State*, Baltimore, 1931, Williams and Wilkins Co.

4. Jones, T. D., and Roche, C. F.: The Transportation of Children With Rheumatic Fever and Heart Disease to a Subtropical Climate. (Read before the Florida Medical Association, Hollywood, Florida, May, 1933.)
5. Graef, I., Parent, S., Zitron, W., and Wyckoff, J.: Studies in Rheumatic Fever: I. The Natural Course of Acute Manifestations of Rheumatic Fever Uninfluenced by "Specific" Therapy, *Am. J. M. Sc.* 185: 197, 1933.
6. Hirsch, A.: *Handbook of Geographical and Historical Pathology*, London, New Sydenham Society, 3, 1886.
7. Newsholme, A.: *Lancet* 1: 589, 1895.
8. Buchanan, W. J.: Acute Rheumatic Fever in the Tropics, *J. Trop. Med.* 2: 128, 1899.
9. Faulkner, J. M., and White, P. D.: The Incidence of Rheumatic Fever and Rheumatic Heart Disease, *J. A. M. A.* 133: 425, 1924.
10. Harrison, T. R., and Levine, S. A.: Notes on the Regional Distribution of Rheumatic Fever and Rheumatic Heart Disease in the United States, *South. M. J.* 17: 914, 1924.
11. Seegal, D., and Seegal, B. C.: Studies in the Epidemiology of Rheumatic Fever, *J. A. M. A.* 89: 11, 1927.
12. Davis, D., and Weiss, S.: Rheumatic Heart Disease: Incidence and Role in Causation of Death, *AM. HEART J.* 7: 146, 1931.
13. McSweeney, C. J.: Studies in Juvenile Rheumatism, *Arch. Dis. Childhood* 6: 367, 1931.
14. A Cardiac Survey of Children in Boston Public Schools, *The Nations Health* 9: No. 12, 1927.
15. Halsey, R. H.: Heart Disease in Children of School Age, *J. A. M. A.* 77: 672, 1921.
16. Cahan, J. M.: Heart Disease Among School Children, *J. A. M. A.* 92: 1576, 1929.
17. Longcope, W. T.: Variations in Manifestations of Rheumatic Fever in Relation to Climate, *Ann. Int. Med.* 5: 401, 1931.
18. Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic, *J. A. M. A.* 89: 1473, 1927.
19. Schwab, E. H., and Schulze, V. E.: Incidence of Heart Disease and Etiological Types in Southern Dispensary, *AM. HEART J.* 7: 223, 1931.
20. Houston, A. N.: An Analysis of 88 Cases of Rheumatic Fever, Comparison With Other Analyses and Discussion, *M. Clin. North America* 11: 1339, 1928.
21. McLean, C. C.: Discussion of "The Etiology of Heart Disease," *South. Med. J.* 26: 219, 1933.
22. Wood, J. Edwin, Jr., and Hart, Andrew D.: Rheumatic Fever in Virginia, Incidence and Clinical Manifestations. (Read before the American Climatological and Clinical Society, Washington, D. C., May 10, 1933.)
23. Coffen, T. H.: The Incidence of Heart Disease in the Pacific Northwest, *AM. HEART J.* 5: 99, 1929.
24. Viko, L. E.: Heart Disease in the Rocky Mountain Region, *AM. HEART J.* 6: 264, 1930.
25. Meloney, H. E., and Kellers, I.: Mitral Stenosis Without Rheumatic Fever in North China, *Arch. Int. Med.* 34: 455, 1924.
26. Anderson, J.: Rheumatic Infections in China, *China Med. J.* 44: 1083, 1930.
27. Maxwell, J. L.: *Diseases of China* (1929), p. 22.
28. Clark, J. Tertius: Rheumatic Fever and Rheumatoid Arthritis: the Geographic Factor, *Lancet* 1: 1169, 1915. Also: *J. Trop. Med. and Hygiene* 33: 249, 1930.
29. Paul, J. R.: Epidemiology of Rheumatic Fever, a Preliminary Report With Special Reference to Environmental Factors in Rheumatic Heart Disease and Recommendations for Future Investigations. For the Am. Heart Assn., 1930, Metropolitan Life Ins. Co. Press, N. Y.

THE INTERPRETATION OF LEAD INVERSION IN BUNDLE-BRANCH BLOCK*

A. D. NICHOL, M.D.
CLEVELAND, OHIO

IN THE interpretation of electrocardiograms representative of bundle-branch block there is a unanimity of opinion only on the characteristic changes produced within the ventricular complex, but the question as to the branch involved in clinical records is yet a controversial subject. Comprehensive reviews of the problem may be found in the publications of Lewis and Rothschild,¹ Lewis,² Fahr,³ Wilson and Herrmann,⁴ Barker,⁵ Wilson⁶ and their collaborators, and Rothberger.⁷ In addition Katz and Ackerman have made the interesting observation that it is possible to transpose the direction of the QRS wave of induced extrasystoles and of experimental right bundle-branch block by changing the position of the dog's heart.^{8, 9} Thus the problem has apparently become more complex. We believe these difficulties have been augmented by the fundamental fact that it is very problematical whether conditions existing in disease can be duplicated with sufficient accuracy to allow conclusions to be drawn from the experimental animal. Obviously it would be more satisfactory if the question could be settled on clinical patients without disturbing their existing circulatory state.

A method satisfying the above requirements is suggested by Wiggers' analysis of experimental extrasystoles.¹⁰ In this study it has been shown: (1) that in asynchronous excitation of the mammalian ventricle systole of the ventricle first excited precedes systole of the opposite ventricle by a definite and measurable interval; (2) that the opposite ventricle shows a slower tension development, i.e., a prolongation of isometric contraction; and (3) that ejection of the ventricle first stimulated precedes ejection of the opposite ventricle. Thus the basis of the present investigation is that, if the left branch of the bundle of His is interrupted, left ventricular ejection will be retarded due to a delay in arrival of the impulse and longer isometric contraction phase and therefore the subclavian arterial pulse will begin to rise later in relation to ventricular excitation than if the conduction mechanism were normal. A priori if the right branch only is involved, left ventricular excitation and contraction will proceed in a normal manner, and ejection, as indicated by the subclavian pulse, should maintain its usual relation to the beginning of ventricular excitation, as

*From the Medical Service of St. Luke's Hospital.

indicated by the QRS of the electrocardiogram. Therefore according to the classical interpretation, the pulse wave of a case with an upright QRS₁ and down QRS₂ (Right BBB) should not be influenced by the bundle-branch block per se, but if the newer conception is correct (Left BBB) there should be a definite delay between the appearance of the QRS in this type of electrocardiogram, and the beginning of the rise of the arterial pulse wave.

METHOD

The electrocardiogram, the subclavian pulse tracing from the left supraclavicular fossa and the apical heart sounds were registered simultaneously. Pulse tracings have been recorded by a Frank segment capsule and sounds by Wiggers' modification of Frank's method.¹¹ The segment capsules were fixed approximately 92.5 cm. from the recording camera and arranged in such a manner that the middle of the reflecting mirrors, the lens of the projecting microscope of the electrocardiogram and the lens of the camera were in the same horizontal plane. The source of light for the capsules was secured by using an arc equipped with the double-slit mechanism of

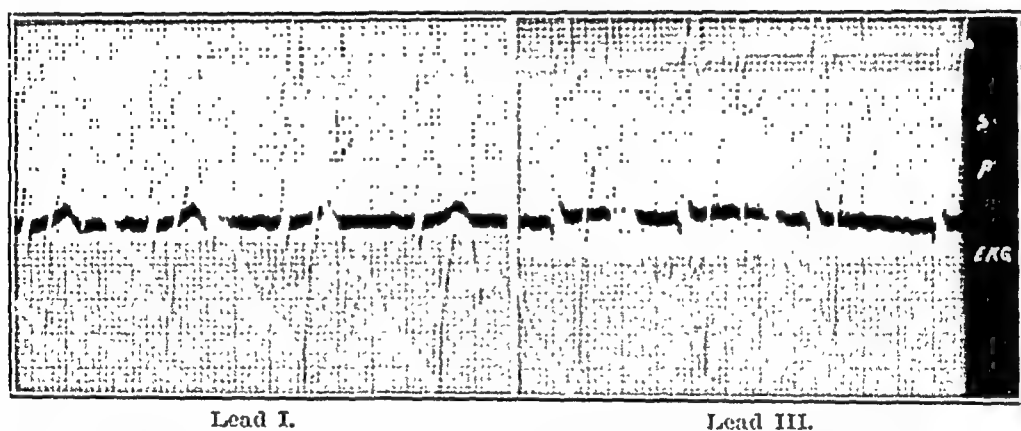


Fig. 1.—Case No. 2172. Lead I: QRS is 0.059 sec. and QE is 0.126 sec. Lead III: QRS is 0.068 sec. and QE is 0.142 sec. Reproduction for effect due to parallax: S, sound wave; P, subclavian pulse tracing; EKG, electrocardiogram.

Katz and Baker¹² which supplies parallel beams. All records were checked for parallax by Garten's method (Fig. 1). No corrections were made when the effect due to parallax was less than 0.004 sec.

After suitable records were secured, lantern slides were made, projected on a screen with a magnification of 10-12 \times and the required intervals measured on the image with a good celluloid ruler which was graduated in half millimeters. Determinations were made on three cycles in both Leads I and III. All measurements were carried out by one observer. The following intervals were determined: (a) the duration of the main ventricular complex of the electrocardiogram, (b) QE or the interval between the beginning of the QRS and the onset of the cardiac ejection phase as evidenced by the rise of the subclavian pulse tracing, and (c) the isometric contraction phase by Wiggers' method (Wiggers and Clough¹³ and Katz and Feil¹⁴). Occasionally it was impossible to measure the isometric period due to imperfect heart sound records or the presence of a doubled second sound. In five of the cases of bundle-branch block the first sound was definitely "reduplicated" or "split," but as Lewis has previously reported,¹⁵ the first component of the "reduplicated" sound preceded the onset of ventricular excitation and could therefore hardly be attributed to asynchronous systole of the ventricles. In such cases we have arbitrarily taken

the beginning of the second component as indicating the onset of ventricular contraction. We believe the error of a single measurement is perhaps not considerably over 0.004 sec.

The most pronounced doubling of the first sound occurred in a case with a P-R interval of slightly more than 0.20 sec. In Case 2206 (Fig. 3) which showed a complete A-V block and ventricular complexes typical of the usual type of bundle-branch block, the first sound varied in intensity with the P-QRS relations and, in addition, there appeared to be a critical As-Vs interval at which doubling of the first sound appeared. These observations would lend no support to a theory that the first component of the doubled sound is caused by ventricular contraction. It probably occurs frequently in bundle-branch block because of the relations of atrial

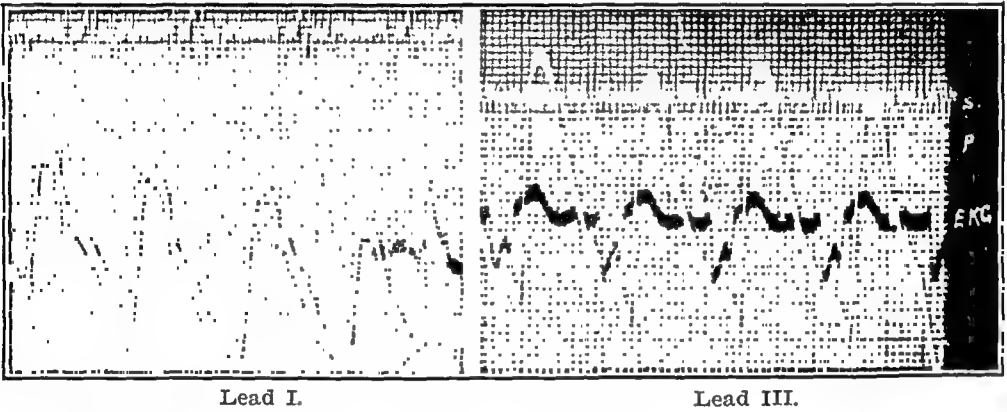


Fig. 2.—Case No. 2276. Lead I: QRS is 0.160 sec. and QE is 0.176 sec. Lead III: QRS is 0.163 sec. and QE is 0.181 sec. Double first sound, S' and S'' .

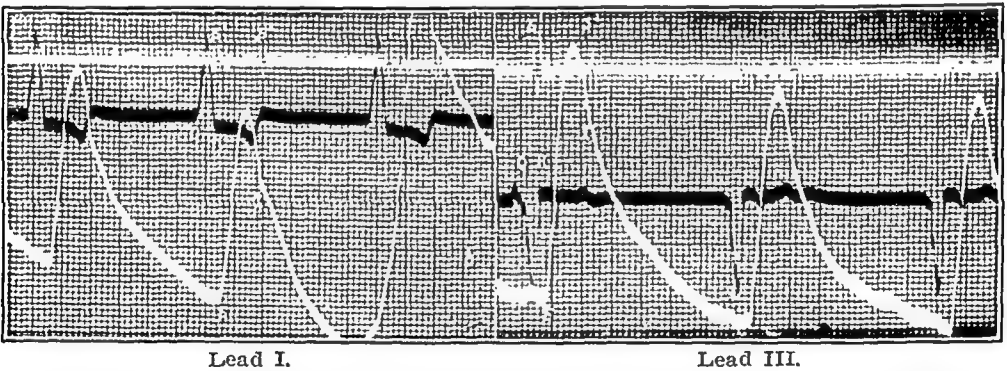


Fig. 3.—Case No. 2206. Lead I: QRS is 0.127 sec. and QE is 0.175 sec. Lead III: QRS is 0.131 sec. and QE is 0.172 sec. The QRS in Lead II is distinctly notched.

and ventricular systole, the mechanism being similar to that present in complete A-V block in which atrial sounds are heard.

No attempt was made to determine the speed of the pulse wave, and in the absence of any gradient for velocity and the impossibility of obtaining the distance of the arterial system involved, we know of no way by which this could be evaluated. It seems probable, however, that any modifying influence from this source would tend to shorten the QE, as our patients with bundle-branch block were over fifty years of age, all but one had an arterial hypertension, and there were definite, though moderate, sclerotic changes in the palpable arteries in all. Some of the pathological controls were in a circulatory state similar to that in the cases of bundle-branch block, yet the QE in the former cases were not significantly different from the average found in their own group. Also if the accepted standards for pulse wave

velocity^{16, 17, 18, 19} are taken as indicating the velocity of the pulse wave in the aorta, it would be necessary to show a tremendous decrease in these figures in order to secure a time interval sufficient to explain the increased QE found in our cases of bundle-branch block.

RESULTS

The intervals previously described, QRS, QE and the isometric period were measured in (a) eighteen normal individuals, (b) seven cases of bundle-branch block in which the QRS was upright in Lead I and downward in Lead III, (c) twenty-two cases with various types of heart disease but with a normal duration of ventricular excitation, and (d) nine cases of heart disease with a prolonged period of ventricular excitation but in which the electrocardiogram was not typical of bundle-branch block.

TABLE I
NORMAL CONTROLS

NUMBER	QE		ISOMETRIC PERIOD	VENTRICULAR RATE
	LEAD I	LEAD III		
1957	0.132 sec.	0.114 sec.	0.069 sec.	70
1994	0.142	0.151	0.065	94
2017	0.119	0.137	0.046	75
2021	0.127	0.127	0.064	72
2026	0.149	0.138	0.070	70
2060	0.119	0.129	0.058	72
2064	0.145	0.134	0.040	52
2065	0.129	0.113	0.065	75
2077	0.151	0.124	0.045	60
2078	0.166	0.163	0.082	75
2080	0.147	0.141	0.071	75
2081	0.134	0.148	0.046	68
2091	0.137	0.153	0.063	60
2172	0.126	0.142	0.050	75
2188	0.134	0.134	0.077	75
2183	0.129	0.114	0.027	66
2184	0.119	0.119	0.036	75
2028	0.120	0.118	0.048	94

The QE values for the eighteen normal individuals of Group A are given in Table I. Fig. 1 is the record from one such case. These individuals were young males between the ages of twenty and thirty years who were leading vigorous lives and who showed no evidence of car-

TABLE II
BUNDLE-BRANCH BLOCK

NUMBER	QE		ISOMETRIC PERIOD	VEN-TRICULAR RATE	ARTERIAL PRESSURE	AGE
	LEAD I	LEAD III				
1954	0.163 sec.	0.165 sec.	0.048 sec.	72	180/112	69
2020	0.195	0.169		76	190/126	62
2069	0.182	0.173		100	170/100	53
2155	0.152	0.162	0.042	94	195/100	57
2229	0.173	0.168	0.080	92	144/96	68
2206	0.175	0.172	0.090	65	168/58	53
2294	0.193	0.176		100	112/86	60

TABLE III
PATHOLOGICAL CONTROLS

NUMBER	QE		ISOMETRIC PERIOD	VEN-TRICULAR RATE	ARTERIAL PRESSURE	AGE	CLINICAL DIAGNOSIS
	LEAD I	LEAD III					
1996	0.086 sec.	0.098 sec.	0.026 sec.	75	110/70	22	Diphtheretic Myocarditis (?).
2048	0.101	0.125		90	130/30	48	Aortic Insufficiency (Luetic).
2054	0.105	0.126	0.039	72	138/90	43	Aortic Aneurysm (Luetic).
1943	0.135	0.138		78	106/78	13	Rheumatic Heart Disease. Mitral Insufficiency.
2032	0.146	0.147	0.056	80	118/90	34	Aur. Fib. Rheu. H. D. Adherent Pericardium (?).
2094	0.132	0.145	0.075	88	106/58	15	Rheumatic Heart Disease. Mitral Stenosis.
2100	0.148	0.148	0.048	94		23	Rheumatic Heart Disease. Mitral Stenosis.
2105	0.112	0.119	0.065	100	110/54	12	Rheumatic Heart Disease. Mitral Stenosis.
2154	0.110	0.115	0.056	100		7	Rheumatic Heart Disease.
2052	0.096	0.084	0.027	124		57	Rheumatic Heart Disease. Aortic and Mitral Stenosis Insufficiency.
2217	0.105	0.116		75	100/70	26	Congenital Heart Disease.
2114	0.116	0.118	0.036	60		9	Congenital Heart Disease.
2045	0.129	0.087	0.027	110	132/86	37	Cardiac Neurosis (?).
2056	0.088	0.092	0.036	140	140/82	14	Exophthalmic Goiter.
2116	0.139	0.144	0.053	75	128/82	24	Paroxysmal Tachycardia.
2171	0.095	0.097	0.038	94	154/72	52	Thyrotoxicosis. Myocardial Disease.
2189	0.099	0.103	0.031	116	152/60	18	Exophthalmic Goiter.
2189	0.127	0.133	0.040	138			Post-thyroidectomy.
2050	0.098	0.115	0.028	96	126/72	52	Arteriosclerotic Heart Disease.
2057	0.113	0.123	0.063	100	158/90	55	Arteriosclerotic Heart Disease.
2075	0.123	0.142	0.066	60	128/96	39	Arteriosclerotic Heart Disease.
2185	0.135	0.141	0.089	68	135/94	23	Hypertensive Heart Disease.
2074	0.116	0.099		34	160/58	68	Arteriosclerotic Heart Disease.

diac or vascular disease. The electrocardiogram in all cases was normal and the QRS varied from 0.049 to 0.093 sec. The arithmetic mean for QE is 0.1347 sec. in Lead I and 0.1333 sec. in Lead III. The corresponding standard deviations of the means are 0.003567 and 0.00348 sec.

The findings in seven cases of bundle-branch block (Group B) appear in Table II. Fig. 2 is the record of one of these. All the individuals in this group had arteriosclerotic heart disease, with varying degrees of cardiac hypertrophy which was preponderantly of the left ventricular type. With one exception all these tracings would un-

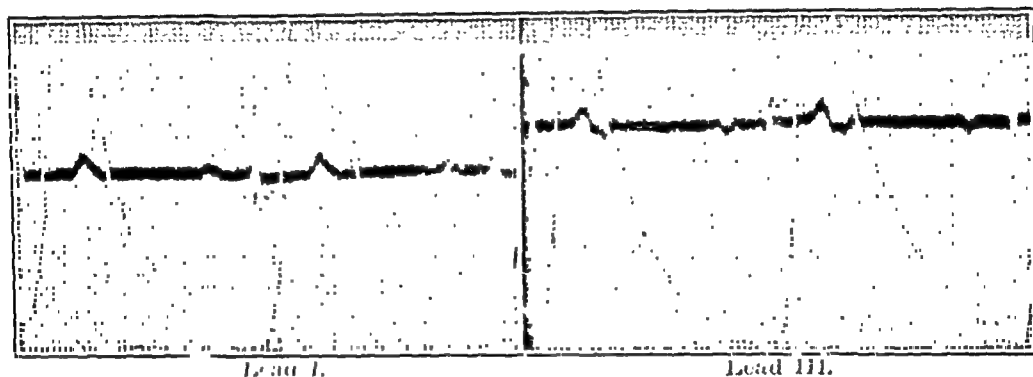


Fig. 4.—Case No. 2074. Lead I: QRS is 0.087 sec. and QE is 0.116 sec. Lead III: QRS is 0.069 sec. and QE is 0.099 sec.

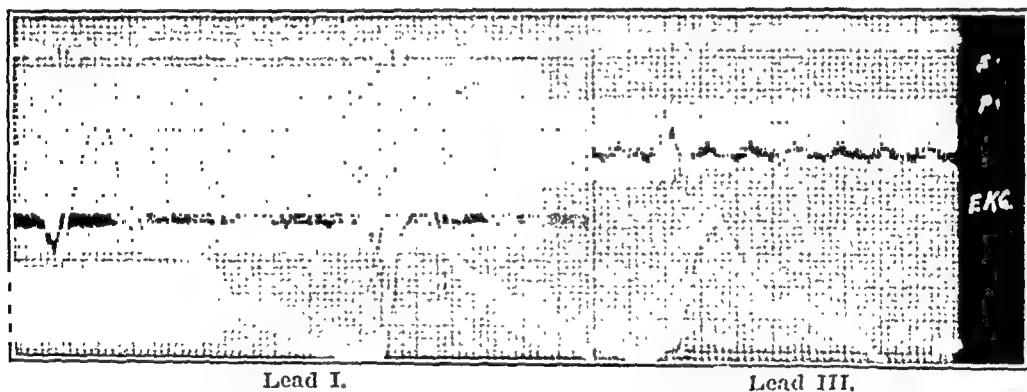


Fig. 5.—Case No. 1992. Lead I: QRS is 0.104 sec. and QE is 0.098 sec. Lead III: QRS is 0.114 sec. and QE is 0.109 sec.

questionably be labelled as bundle-branch block, i.e., a supraventricular QRS more than 0.10 sec. in duration, opposite in direction in Leads I and III, with a distinct notch in the main ventricular complex and with T-waves opposite in direction to the QRS. Case 2206 (Fig. 3) probably represents a nodal rhythm but the QRS and T-waves are uniform and satisfy the remaining requirements for bundle-branch block. This case therefore has been included with the above group, representing the usual type (Right BBB, old terminology). The arithmetic mean for QE in the group is 0.1761 sec. in Lead I and 0.1693 sec. in Lead III. The corresponding standard deviations for the means are 0.0058 and 0.0018 sec.

The determinations on the group of controls with heart disease (Group C) are given in Table III. The duration of QRS was less than 0.10 sec. in all leads. The analysis of these pathological cases would be of greater value if they could be grouped according to age or type of heart disease. Unfortunately our clinical material was too small for this purpose. Fig. 4 is a record illustrating the normal time relations of the subclavian pulse in a case with a marked left ventricular preponderance and a 2:1 A-V block. The arithmetic mean for QE in the group is 0.1154 sec. in Lead I and 0.1198 sec. in Lead III. The corresponding standard deviations for the means are 0.00383 and 0.00426 sec.

No attempt was made to analyze statistically the findings in the cases with a prolonged period of ventricular excitation (Group D). Some of these records were very suggestive of bundle-branch block but have not been included in that group because the QRS were not entirely typical. Fig. 5 is of interest because of its relation to the unusual type of bundle-branch block. T-waves are not present and the ventricular rate is 33, but the QRS is definitely notched, widened and downward in Lead I and upright in Lead III. The ventricular excitation wave in this case is therefore much the same as that present in the unusual type of bundle-branch block (Left BBB, old terminology). The QE is 0.098 sec. in Lead I and 0.109 sec. in Lead III, and these values fall within the limits of Group C.

DISCUSSION

What effect has the aberrant path of the excitation wave on the mechanics of ventricular systole in clinical bundle-branch block? Wiggers in his study of artificially induced extrasystoles concludes: "When a local artificial stimulus is applied to any portion of the ventricular surface, the impulse spreads somewhat radially from the point of stimulation and induces a series of local fractionate contractions responsible for the initial slow rise of intraventricular pressure. This continues until the impulse has reached the His-Tawara system and has been conducted by that system to the unexcited portions of the ventricle. Consequently, two different contraction processes almost imperceptibly merge, viz., (a) a localized fractionate contraction occasioned by a relatively slow fiber-to-fiber excitation, and (b) a more generalized contraction of the remaining ventricle excited via bundle branches in more rapid sequence. Inasmuch as the latter also starts in a fractionate manner isometric contraction and total systole are prolonged."¹⁰ It is probable that this same process is present in bundle-branch block due to the fiber-to-fiber conduction of the excitation wave before it reaches the distal portions of the bundle branch which is blocked. The statistical analysis of the isometric periods in the cases of bundle-branch block is not conclusive because of the small number, but it indicates that the mean of the isometric periods in our cases

of bundle-branch block is not significantly different from that of the normal group. Thus after the excitation wave reaches the terminal portions of the His-Tawara system, ventricular systole probably progresses in a normal manner, and the delay in the incidence of the subclavian pulse is probably due to the decreased speed and lengthened path of the excitation wave as it is conducted through or around the interventricular septum. The analysis of our cases shows that the beginning of the rise of the subclavian pulse occurred, on an average, definitely later in individuals with the usual type of bundle-branch block (Right BBB, old terminology) than in normal individuals or in patients with heart disease but with a normal duration of ventricular excitation. This result is statistically significant when tested by the method of Fisher.²⁰ Also in one instance in which the QRS was widened, notched and downward in Lead I and upright in Lead III, the value for QE was within the limits of QE for the group with heart disease but with a normal duration of ventricular excitation. If the left ventricle in our cases of bundle-branch block was stimulated in a normal manner, then we are unable to explain the increase in the value of QE, which amounts to, in an average, 0.0414 sec. as compared to the normal, or 0.0607 sec. as compared to the pathological controls. But, if these cases represent a left bundle-branch block, the increased value for QE becomes readily explainable by the aberrant path of the excitation wave. We believe therefore that the left ventricle is activated last in the usual type of bundle-branch block. This is in accordance with the original idea of Fahr and the more recent conclusion of Wilson and Barker.

CONCLUSIONS

A new method of attacking the problem of bundle-branch block has been described.

In our cases of bundle-branch block with an upright QRS₁ and downward QRS₂, the incidence of the subclavian pulse was definitely delayed. Therefore it seems most probable that this type of electrocardiogram represents a left rather than a right bundle-branch block.

I wish to express my indebtedness to Dr. R. Dominguez for useful criticism and for the statistical analysis of the data. Dr. Harold Feil has given me the opportunity to study one of his cases and has offered numerous suggestions as to the technic employed. Dr. Carl J. Wiggers has kindly and critically reviewed the technic and the manuscript.

REFERENCES

1. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart, *Phil. Tr. Roy. Soc. B.* 206: 181, 1915.
2. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, London, Shaw and Sons, Ltd.
3. Fahr, G.: Analysis of the Spread of Excitation in the Human Ventricle, *Arch. Int. Med.* 25: 146, 1920.
4. Wilson, F. N., and Herrmann, G. R.: Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period in the Dog Heart, *Heart* 8: 229, 1921.

5. Barker, P. S., MacLeod, A. G., and Alexander, J.: The Excitatory Process Observed in the Human Heart, *AM. HEART J.* 6: 720, 1930.
6. Wilson, F. N., MacLeod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, *AM. HEART J.* 6: 637, 1931.
7. Rothberger, C. J.: Normal und Pathologphysiologie der Rhythmie und Coördination des Herzens, *Ergeb. d. Physiol.* 32: 472, 1931.
8. Katz, L. N., and Ackerman, W.: Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, *J. Clin. Investigation* 2: 1221, 1932.
9. Ackerman, W., and Katz, L. N.: Reversal in Direction of the QRS Complex of Experimental Right Bundle-Branch Block With Change in the Heart's Position, *AM. HEART J.* 8: 491, 1933.
10. Wiggers, C. J.: Muscular Reactions of the Mammalian Ventricle to Artificial Stimuli, *Am. J. Physiol.* 73: 346, 1925.
11. Idem: *The Circulation in Health and Disease*, Philadelphia, 1923, ed. 2, Lea & Febiger.
12. Katz, L. N., and Baker, W. R.: Adjustable Double-Slit Lamp for Use in Multiple Optical Registrations, *J. Lab. & Clin. Med.* 10: 47, 1925.
13. Wiggers, C. J., and Clough, H. D.: Physiological Investigations Into the Dynamic Action of the Heart in Functional Cardiac Disorders, *J. Lab. & Clin. Med.* 4: 624, 1919.
14. Katz, L. N., and Feil, H. S.: Clinical Observations on the Dynamics of Ventricular Systole. I. Auricular Fibrillation, *Arch. Int. Med.* 32: 672, 1923.
15. Lewis, T.: Illustrations of Heart Sound Records, *Quart. J. Med.* 6: 441, 1912.
16. Hafkesbring, R., and Ashman, R.: Pulse Wave Velocities in Ninety Subjects, *Am. J. Physiol.* 100: 89, 1932.
17. Beyerholm, O.: Pulse Wave Velocities, *Act. Med. Scand.* 67: 202, 1927.
18. Bramwell, J. C., and Hill, A. V.: Velocity of the Pulse Wave in Man, *Proc. Roy. Soc.* 93: 298, 1922.
19. Fulton, J. S., and McSwiney, B. A.: Pulse Wave Velocity and Extensibility of Radial and Brachial Artery in Man, *J. Physiol.* 69: 386, 1930.
20. Fisher, R. A.: *Statistical Methods for Research Workers*, Edinburgh, 1928, ed. 3, Oliver and Boyd.

COMPLETE HEART-BLOCK IN HYPERTHYROIDISM FOLLOW-
ING ACUTE INFECTIONS: A REPORT OF SIX CASES
WITH NECROPSY FINDINGS IN ONE CASE*

AUSTIN C. DAVIS, M.D., AND HARRY L. SMITH, M.D.
ROCHESTER, MINN.

THE high incidence of irregular cardiac action is one of the striking features of hyperthyroidism. The arrhythmia consists mainly of auricular fibrillation, however, either paroxysmal or permanent, and to a less extent, of auricular flutter. These forms of arrhythmia depend on disturbance of auricular contractility. Defective auriculo-ventricular conductivity is much less frequent, and complete auriculo-ventricular dissociation is uncommon. In a review of the literature on the etiology of heart-block and on arrhythmia occurring with hyperthyroidism, we could find only four reports of complete heart-block associated with hyperthyroidism. Merklen,¹¹ in 1882, reported the case of a woman, aged twenty-seven years, who had had exophthalmic goiter for six years, and who had attacks of ventricular standstill of four or five seconds' duration with convulsive seizures. These attacks had developed eight days following an acute cold, with sore throat. There also was fever which could not be explained by the physical findings. The seizures occurred repeatedly over a period of two days, and their cessation was associated with recovery from the arrhythmia. In 1915 de Vries Reilingh¹⁴ reported a case of Basedow's disease with heart-block and Stokes-Adams syndrome, in which the cardiac action returned to normal within ten days. Dameshek,⁴ in 1924, in an analysis of the instances of arrhythmia reported in a series of 141 cases of hyperthyroidism, found electrocardiographic evidence of complete auriculoventricular dissociation in two cases: that of a woman, aged twenty-six years, and that of a man, aged twenty-nine years.

Reports of less severe degrees of defect in conduction have been somewhat more numerous. Lewis,¹⁰ in 1913, referred to a patient with a history of repeated attacks of rheumatic fever, who had partial heart-block following thyroidectomy for exophthalmic goiter, and, subsequently only prolonged auriculoventricular conduction time. Krumbhaar⁹ noted two cases in which the P-R interval was prolonged, in a series of fifty-one cases studied. Willius, Boothby and Wilson,¹⁷ in a study of a series of 298 cases, found one in which there was a P-R interval of twenty-eight hundredths of a second. In the study made by Dameshek⁴ in 1924 there were, besides the two cases of com-

*From the Division of Medicine, The Mayo Clinic.

plete heart-block, two cases in which conduction time was delayed. In 1929 Andrus,¹ in a series of eighty-six cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism, found one case of heart-block, the type of which he did not specify. Eason,⁵ in 1930, described the case of a young woman who had exophthalmic goiter, and who had fever of several weeks' duration following tonsillectomy; subsequent to the febrile period, a syncopal attack, with associated arrhythmia, occurred. The electrocardiogram gave evidence of partial heart-block; that is, a prolonged P-R interval with occasionally dropped ventricular complexes. The patient recovered satisfactorily from the arrhythmia. Cameron and Hill,³ in 1932, reported two cases of partial heart-block in association with exophthalmic goiter; the patients were young women. In one case the heart-block was present three weeks following an attack of tonsillitis; in the other case the heart-block developed twenty-four days following the onset of acute tonsillitis and four days following tonsillectomy. The authors called attention to the possibility of the infection of the throat being an etiological factor in the production of the heart-block.

Investigators, as follows, have reviewed series of cases of hyperthyroidism and have not found evidence of disturbed auriculoventricular conductivity: Smith and Colvin,¹³ 100 cases; White and Aub,¹⁶ twenty-seven cases; Kerr and Hensel,⁸ fifty-eight cases. The experience of Goodall and Rogers,⁶ however, was at variance with these findings; they found the P-R interval to be prolonged in 242 cases in a series of 787 cases of hyperthyroidism which they studied. There was, however, no instance of a higher grade of defect in conduction.

The cases in which electrocardiograms made at The Mayo Clinic since 1923 gave evidence of complete heart-block were reviewed. Six of the patients had exophthalmic goiter. No cases of adenomatous goiter with hyperthyroidism in which complete heart-block occurred were found in this period of time. This was contrary to expectation when the study was undertaken. We had anticipated a coincidental association of complete heart-block resulting from arteriosclerotic heart disease and hyperthyroidism and also that this association would occur less frequently with exophthalmic goiter than with adenomatous goiter with hyperthyroidism, since the latter occurs at a more advanced average age.²

REPORT OF CASES

CASE 1.—A woman, aged twenty-two years, came to the clinic September 13, 1924, with exophthalmic goiter of one and a half years' duration. She had not received digitalis. On account of a mild, acute infection of the upper part of the respiratory tract, operation was delayed until September 30, when subtotal thyroidectomy was performed. Except for persistent fever until the eighth postoperative day, convalescence was uneventful. On that day an epileptiform seizure suddenly developed and was accompanied by marked bradycardia. The attacks recurred for two

days, and repeated electrocardiograms gave evidence of complete auriculoventricular dissociation. Conduction time became normal October 17, and subsequently the patient's convalescence was without noteworthy incident. Two years later she reported that she was in good health.

CASE 2.—A woman, aged twenty-seven years, came to the clinic September 13, 1922, on account of severe exophthalmic goiter of five months' duration. October 3 the left superior thyroid vessels were ligated, and October 10 the corresponding vessels on the right side were ligated. The patient did not return for further operation until February 22, 1923. Three days after her return acute follicular tonsillitis with fever developed; it persisted for five days. Partial thyroidectomy was performed March 17. The postoperative reaction was rather severe, the pulse was persistently rapid, and the temperature was elevated until the eighth postoperative day, when the pulse rate suddenly dropped from 140 to 72, and to 36 the following day. A syncope attack occurred on that day, with unconsciousness of a few seconds' duration; there was marked pallor, but no convulsion or muscular twitching. Fifteen such attacks occurred during the day. The electrocardiogram revealed complete auriculoventricular dissociation. Normal conduction time was not established until six days later. Twenty-five days following thyroidectomy the patient was dismissed from observation, and three months later she reported that she was in good health.

CASE 3.—A man, aged thirty-five years, came to the clinic March 11, 1925, on account of severe exophthalmic goiter of one year's duration, and mild congestive heart failure. An electrocardiogram revealed rapid auricular fibrillation. Four days later scarlet fever developed, and the temperature was elevated for four days. March 29 the fever recurred, and there was evidence of multiple arthritis. March 31 the pulse became regular and its rate dropped abruptly to 40 each minute. The patient appeared to be extremely ill but he did not lose consciousness. April 1, an electrocardiogram gave evidence of a ventricular rate of 47 and of auricular fibrillation with regular ventricular rhythm. The QRS complex represented an interval of twelve-hundredths of a second. The pulse remained regular; its rate was between 40 and 47 for three days and then gradually increased and again became irregular. April 9, the QRS complex represented an interval of normal duration. May 18, the right lobe of the thyroid gland was removed. A severe reaction followed, but there was no evidence of recurrence of the heart-block.

CASE 4.—A woman, aged fifty-three years, came to the clinic January 21, 1923, with exophthalmic goiter of ten months' duration. The basal metabolic rate was +49 per cent. She had not received digitalis or iodine. A week later an acute infection of the upper part of the respiratory tract, with acute tonsillitis and fever, developed. This persisted for a week. For a month she complained of a cold, but there were no findings to substantiate the complaint. The fever recurred March 4, but the physical findings were still negative. March 6 the pulse rate suddenly dropped from 116 to 70, and the patient became weak and nauseated, and vomited. An electrocardiogram revealed complete auriculo-ventricular dissociation, and this was found again March 7 (Fig. 1).

The patient died March 10. The post-mortem findings were as follows: the heart weighed 257 gm. and was not enlarged. Nothing unusual was noted about the epicardial surfaces. The endocardial surfaces were smooth, and everywhere intact. There were no gross lesions of the valve leaflets, cusps, or chordae tendineae. The walls of the ventricles were of normal thickness. The left ventricle was thought to be slightly dilated. On cut section the myocardium was normal in color and consistence.

Sections were taken from various portions of the heart for microscopic study. Sections taken from the walls of the auricles, and in the region of the sino-auricular node, appeared normal and stained well. Sections taken from different portions of the wall of the left ventricle appeared normal. Sections taken through the auriculoventricular node and bundle contained, especially in the ventricular portion

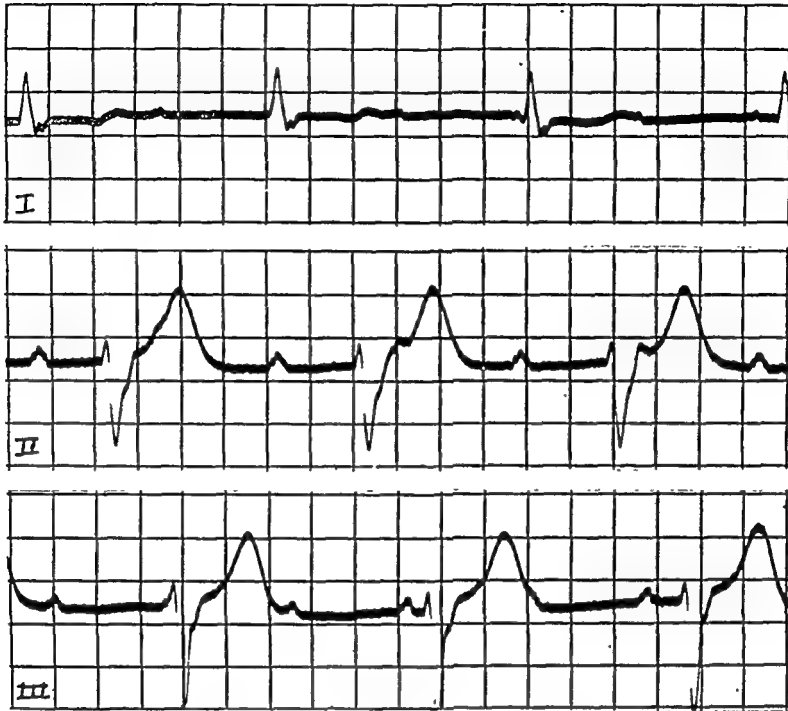


Fig. 1.—Complete auriculoventricular dissociation. Ventricular rate 50 beats a minute; auricular rate, 110.

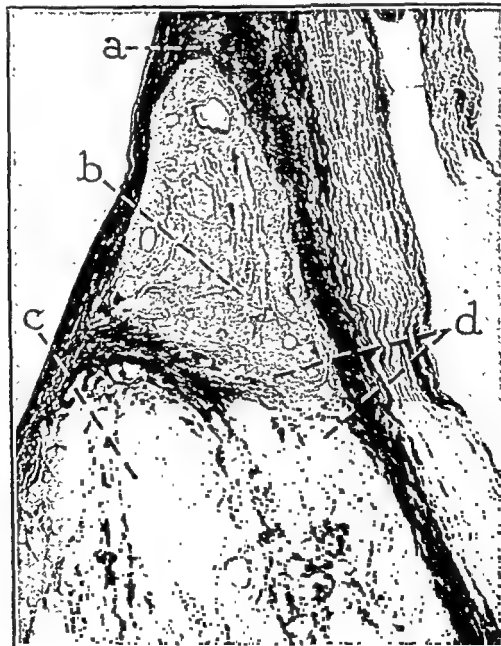


Fig. 2.—*a*, Membranous portion of the interventricular septum; *b*, auricular ventricular bundle; *c*, muscular portion of interventricular septum; *d*, areas of cellular infiltration ($\times 35$).

of the bundle, and also in adjacent structures, extensive cellular infiltration (Fig. 2). This process consisted of cellular foci composed of numerous polymorphonuclear leucocytes (Fig. 3), and considerable numbers of small mononuclear cells. Many dilated blood vessels were present. This portion of the auriculoventricular bundle and the adjacent tissues were somewhat edematous. The cellular infiltration was most marked at the juncture of the membranous with the muscular portion of the interventricular septum. The infiltration extended for a considerable distance down into the interventricular septum. There were several regions of leucocytic infiltration throughout the wall of the right ventricle.

In sections taken at the juncture of the membranous and muscular portions of the interventricular septum, where the leucocytic infiltration was most extensive, and stained with Brown Gram stain, were some gram-positive bacteria (Fig. 4), which were believed to be either diplococci, or streptococci in short chains. These bacteria were found in the ventricular portion of the auriculoventricular bundle and its adjacent structures. They were most numerous just beneath the endocardium.

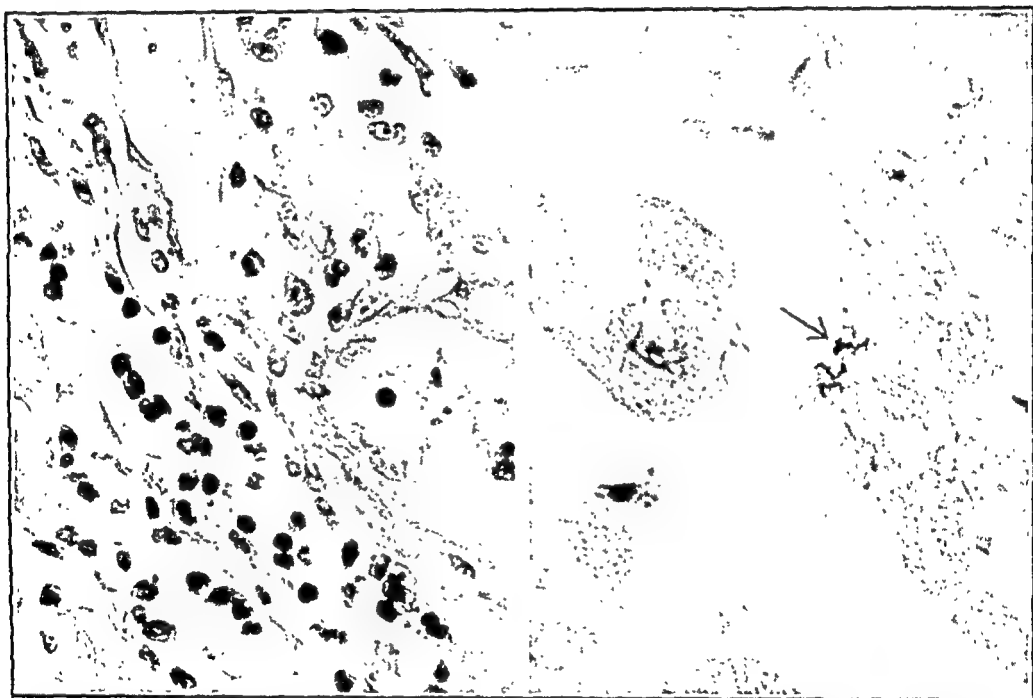


Fig. 3.—Higher magnification of a section taken from area *d* in Fig. 2. Numerous polymorphonuclear leucocytes, a few small mononuclear cells, and many dilated blood vessels and considerable edema, are evident. Hematoxylin and eosin ($\times 700$).

Fig. 4.—Section taken from area *d* in Fig. 2, stained with Brown Gram stain. The arrow points to what is believed to be a short chain of streptococci ($\times 500$).

The thyroid gland weighed 58 gm., and on microscopic examination was seen to have undergone rather marked parenchymatous hypertrophy. The thymus was moderately hypertrophied. The liver was somewhat atrophic; its weight was 1,284 gm. Other structures examined were essentially normal.

CASE 5.—A woman, aged sixty-three years, came to the clinic June 12, 1929, on account of exophthalmic goiter of two years' duration. She also had mitral stenosis. She had received digitalis continuously for five months, until the time of her admission to the clinic. She had congestive heart failure, and the electrocardiogram gave evidence of complete auriculoventricular dissociation. There was no history or evidence of recent acute infection. Administration of digitalis was discontinued, and two weeks later conduction time was normal. August 7 lobectomy was per-

formed. Six months later the patient was reexamined; the P-R interval was then twenty-eight hundredths of a second, and the basal metabolic rate was -11 per cent.

CASE 6.—A woman, aged sixty-five years, came to the clinic February 19, 1929, on account of exophthalmic goiter. She had received digitalis continuously for four months, to the time of her admission at the clinic; we found that she had complete heart-block. Administration of digitalis was discontinued, and five days later there was a regular ventricular response to auricular contraction. However, there was delayed auriculoventricular conduction time, and this persisted. Subtotal thyroidectomy was performed March 6. An electrocardiogram, made seven days later, disclosed normal conduction time.

In all of the six cases reported, the Wassermann test was negative, and in Cases 1, 2, 3 and 4 throat cultures for *Corynebacterium diphtheriae* (*Bacillus diphtheriae Klebs*) were negative.

COMMENT

Judging from any evidence which we were able to find concerning either the morbid anatomy or functional disturbance of the heart in the presence of hyperthyroidism, there would seem to be no reason for hyperthyroidism in itself to result in interference with auriculoventricular conductivity. No distinctive type of cardiac lesion has been accepted generally as characteristic of hyperthyroidism. That non-specific myocardial lesions occur more frequently and are of greater extent in cases of hyperthyroidism than in control series has been observed repeatedly in the study of the pathological changes in the heart in cases of hyperthyroidism.^{12, 15} In exceptional cases there are regions of mononuclear infiltration and destruction of muscle fiber, which, if situated in or near the bundle of His could result in loss of auriculoventricular conductivity.

Ordinarily, in cases of hyperthyroidism, there is no definite change in auriculoventricular conduction time, in spite of the accelerated cardiac rate and the stimulated general physiological activity. Although there has been some divergence of opinion concerning the length of the P-R interval in the presence of hyperthyroidism, Joll⁷ concluded, after a review of the published evidence, that there is no shortening of the auricular period and that in a few cases there may even be a degree of heart-block. In the reported cases to which he referred, however, there was no evidence to indicate that in those cases in which the interval was increased, hyperthyroidism was the only etiological factor. In each of the first four cases reported in the series of six reviewed from the records of The Mayo Clinic, an acute infection immediately preceded or accompanied the onset of the heart-block. In Case 4, the pathological findings were conclusive evidence of the mode of production of the heart-block, and were indicative of the disturbance of mechanism in Cases 1, 2 and 3, in all of which the sequence of events preceding the onset of the heart-block was similar. In Case 3, the clinical course of the patient subsequent to recovery from the heart-block also would tend to indicate the presence of a localized inflammatory lesion in or near the auriculoventricular bun-

dle, secondary to scarlet fever. The patient gradually recovered from the heart-block without any appreciable decrease in the severity of the hyperthyroidism, and later, following lobectomy and a severe postoperative reaction evidence of recurrence of defective auriculo-ventricular conductivity did not develop.

The part played by acute infection in the production of interference with auriculoventricular conductivity has been thoroughly established by extensive investigations of the pathological anatomy. In the literature are reports of numerous cases in which the development of heart-block has been conclusively explained by the presence of localized inflammation, of various degrees, in the auriculoventricular bundle or adjacent to it. Such processes have accompanied infections of many types, such as tonsillitis, rheumatic fever, diphtheria, pneumonia, gonorrheal septicemia, and infection of the blood stream from various sources. At least four of the reported cases of hyperthyroidism with associated heart-block referred to in the literature, namely, those of Merklen,¹¹ Eason,⁵ and Cameron and Hill,³ would seem to fall into the same category as the first four cases of the series which we have reported in this paper, so far as recent infection is concerned. In the cases brought to attention by Eason, and by Cameron and Hill, the patients had had acute tonsillar infection, and in the case referred to by Merklen an acute infection of the upper part of the respiratory tract shortly preceded the onset of the heart-block. Furthermore, in all of these cases the patients were young, and gave no evidence of having suffered previous cardiac injury.

With exophthalmic goiter, the patients display a pronounced susceptibility to acute tonsillitis, and although most of them recover promptly and satisfactorily from the infection, at times the reaction is severe. It would seem possible that fatigue from overwork, or perhaps an intrinsic metabolic disturbance, would result in lowered resistance to metastatic infection or toxemia, with greater susceptibility to such complications as developed in Case 4 of those here reported. This explanation has been suggested by Rake and McEachern.¹² Yater¹³ stated that rabbits given injections of thyroxine are more susceptible to infection, that focal necrosis readily develops throughout the heart, and that other lesions indicating inability of the myocardium to cope with infection appear in cases of hyperthyroidism.

The occurrence of auriculoventricular dissociation in Case 5 is reasonably explained on the basis of the effect of digitalis on a previously injured auriculoventricular bundle. Chronic mitral valvular disease was present in this case, and administration of digitalis for a month resulted in complete auriculoventricular dissociation, which disappeared following discontinuance of the treatment with digitalis. The probability that the bundle had been injured prior to the time of

the treatment with digitalis is enhanced by the fact that seven months after occurrence of the auriculoventricular dissociation, conduction time was slightly prolonged at the time when the low basal metabolic rate, previously mentioned, was determined. In Case 6, although no clinical evidence of intrinsic cardiac injury was present, the age of the patient made probable the same explanation as applies in Case 5. In Case 6 the patient had taken digitalis continuously for five months prior to examination at the clinic and when administration of digitalis was discontinued, the heart-block decreased in severity, although it was not known that it subsided until following thyroidectomy.

SUMMARY

Six cases of exophthalmic goiter in which complete auriculoventricular dissociation occurred were observed at The Mayo Clinic. Three of the patients had had acute tonsillitis shortly preceding the onset of the arrhythmia and one patient had had scarlet fever. In the one fatal case, necropsy revealed an inflammatory lesion involving the region of the bundle of His, in which we were able to demonstrate gram-positive bacteria which we believed to be either diplococci or streptococci in short chains. In the two cases of the series in which development of the heart-block was not associated with acute infection, there is reason to believe that the heart-block was precipitated by the effect of digitalis on a previously injured auriculoventricular bundle. In those cases in which acute infection was present, evidence is advanced to indicate that the hyperthyroidism predisposed the patient to the development of acute infection, and also to secondary myocardial involvement which resulted in the occurrence of heart-block.

REFERENCES

1. Andrus, E. C.: Heart Failure With Hyperthyroidism, *New York State J. Med.* 29: 661, 1929.
2. Boothby, W. M.: *Diagnosis and Treatment of the Diseases of the Thyroid Gland*, Oxford Med. pt. 2, 3: 905, 1922.
3. Cameron, J. D. S., and Hill, I. G. W.: Heart-Block in Toxic Goiter: a Report of Two Cases, *Edinburgh M. J.* 39: 37, 1932.
4. Dameshek, William: The Heart in Hyperthyroidism, *Boston M. & S. J.* 190: 487, 1924.
5. Eason, John: Toxic Goitre and Some Complications, *Edinburgh M. J.* 37: 54, 1930.
6. Goodall, J. S., and Rogers, Lambert: The Electrical and Histological Manifestations of Thyrotoxic Myocarditis, *Brit. M. J.* 1: 1141, 1927.
7. Joll, C. A.: *Diseases of the Thyroid Gland*, St. Louis, 1932, p. 467, The C. V. Mosby Co.
8. Kerr, W. J., and Hensel, G. C.: The Cardiovascular System in Thyroid Disease, *Arch. Int. Med.* 31: 398, 1923.
9. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goitre, *Am. J. M. Sc.* 155: 175, 1918.
10. Lewis, Thomas: Physical Signs of Myocardial Involvement, *Brit. M. J.* 1: 484, 1913.
11. Merklen: Accidents aigus le cours d'un goitre exophthalmique datant de six ans; fièvre, diarrhée, hyperesthésie générale, intermittences prolongées du cœur suivies d'accès épileptiformes; guérison des phénomènes aigus, *Bull. Soc. clin. de Par.* 5: 53, 1882.

12. Rake, Geoffrey, and McEachern, Donald: A Study of the Heart in Hyperthyroidism, *AM. HEART J.* 8: 19, 1932.
13. Smith, F. J., and Colvin, L. T.: Certain Cardiovascular Features of Hyperthyroidism, *Ann. Clin. Med.* 5: 616, 1927.
14. de Vries Reilingh, D.: Een zeldzame stoornis in de hartwerkzaamheid bij morbus Basedowii, *Nederl. Tijdschr. v. Geneesk.* 2: 1425, 1915.
15. Weller, C. V., Wanstrom, R. C., Gordon, Harold, and Bugher, J. C.: Cardiac Histopathology in Thyroid Disease. Preliminary Report, *AM. HEART J.* 8: 8, 1932.
16. White, P. D., and Aub, J. C.: The Electrocardiogram in Thyroid Disease, *Arch. Int. Med.* 22: 766, 1918.
17. Willius, F. A., Boothby, W. M., and Wilson, L. B.: The Heart in Exophthalmic Goiter and Adenomatous Goiter With Hyperthyroidism, *Med. Clin. N. Amer.* 7: 189, 1923.
18. Yater, W. M.: Discussion, *AM. HEART J.* 8: 144, 1932.

Department of Clinical Reports

STOKES-ADAMS DISEASE TREATED WITH EPHEDRINE; FINAL REPORT OF A CASE*

CHARLES S. HIGLEY, M.D., AND ROBERT M. STECHER, M.D.
CLEVELAND, OHIO

IN 1928 one of us⁶ reported in this JOURNAL a case of Stokes-Adams disease with complete cessation of attacks after the use of ephedrine by mouth. The patient was further observed by us up to the time of his death October 20, 1932. A review of the case with the necropsy findings is given here.

Summary of first admission: J. M., a sixty-five-year-old white laborer, was admitted to the Medical Service at City Hospital, September 27, 1927, complaining of fainting attacks. His present illness began eight days before admission when he suddenly became dizzy and fainted. Recovery was prompt and complete, but similar attacks recurred with increasing frequency and on admission were occurring at intervals of several minutes. His past history was essentially negative. There was no history of diphtheria or syphilis. The patient was accustomed to heavy work and had been a hard drinker. Physical examination revealed a well-nourished and well-developed adult male, resting comfortably in bed. He was having frequent attacks which lasted from fifteen to twenty seconds, in which he showed mental confusion and inability to talk. His face assumed a staring expression, and there was loss of consciousness followed by convulsions. During the attacks his skin became blanched and there was complete cessation of heart sounds, cardiac activity and peripheral pulses. The heart action was resumed with a powerful precordial heave, a distinct flushing of the skin and a sudden return of consciousness. The pulse rate after the attacks was 24 per minute. The chest was emphysematous and the apex impulse could not be definitely localized at any time. The heart sounds were loud and of good quality, and there was a systolic murmur at the apex. Blood pressure was 140/56 mm. Blood Wassermann reaction was negative.

Electrocardiograms taken on admission during one of his attacks showed consecutive periods of ventricular asystole of 7.4 seconds, 3.4 seconds and 10.2 seconds. Later cardiograms taken after the patient had been given ephedrine showed left ventricular preponderance, complete heart-block with regular rhythm. Ventricular rate 25; auricular rate 58 per minute.

Course: The patient was first treated with 10 minims (0.6 c.c.) of 1:1000 solution of epinephrine subcutaneously during attacks. This gave him relief for several hours. Thirty mg. of barium chloride were given three times a day for six days, but this was discontinued because of lack of appreciable effect. He was then given 30 mg. of ephedrine sulphate three times daily by mouth. This gave him relief from the attacks, and in one week the individual dose was cut to 20 mg. He had no more attacks and in two weeks the medication was discontinued. The patient remained symptom free during the ensuing ten weeks and was discharged.

*From the Medical Clinic of Western Reserve University at Cleveland City Hospital.

Subsequent course: The patient was next seen by us in September, 1928, when he returned to the hospital because of a recurrence of his attacks and on admission showed essentially the same picture as on the previous admission. The medication consisted of 30 mg. of ephedrine hydrochloride three times daily by mouth. There was relief of the symptoms and the patient was discharged on this dosage and followed in the Out-Patient Department until May, 1932, when he was readmitted to the Medical Service, complaining of loss of vision.

Physical examination at this time showed a senile white male who was not acutely ill. Both eyes showed opacities of the lens. There was marked dental caries. The pharynx was normal and the tonsils were atrophic. The thyroid was not palpable. The chest was emphysematous and the breath sounds were normal. No râles were heard. The left border of cardiac dullness was 8 cm. from the mid-sternal line and no murmurs were heard. There were occasional extrasystoles. The

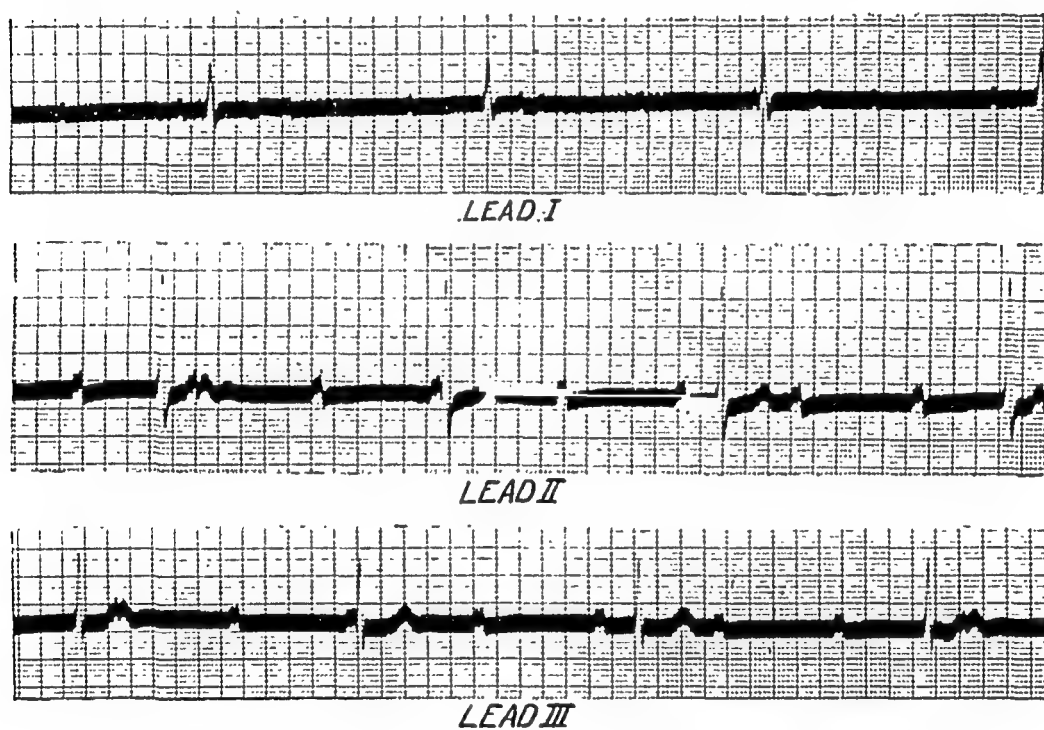


Fig. 1.—Electrocardiogram taken May 26, 1932, showing complete heart-block. Auricular rate 60, ventricular rate 25.

pulse rate was about 26 per minute. Blood pressure was 130/54 mm. The patient showed no signs of cardiac failure. The peripheral vessels were markedly sclerotic. The reflexes were physiological.

Electrocardiograms taken May 26, 1932, showed complete heart-block. The T-wave was upright in all leads. There was no prolongation of the QRS interval. Auricular rate 60, ventricular rate 25 per minute (Fig. 1).

Course: The patient was given 30 mg. of ephedrine sulphate daily. On this dose he was apparently free from attacks and the heart rate remained at about 26 per minute. He was transferred to the Ophthalmological Service and an iridectomy of the right eye was done August 12. One week later he had several attacks and the dose of ephedrine was raised to 25 mg. twice daily. This seemed to control his symptoms moderately well, and September 9 the cataract in the left eye was extracted. Two weeks later it was found necessary to increase the dose of ephedrine to 50 mg. twice daily. He seemed improved and on October 3 a discision of the

left eye was done. Sixteen days later he had a recurrence of frequent Stokes-Adams attacks. The heart rate decreased to 12 per minute between attacks, and he became quite cyanotic and complained of sharp pain in the right arm. Large doses of caffeine-sodium-benzoate and epinephrine were given subcutaneously, but the patient died the next day during an attack.

Anatomical Findings.—The autopsy was performed thirty-six hours after death by Dr. T. T. Frost. We are indebted to him and to Dr. David Seecef for the pathological description of this case.

Heart: The heart weighed 550 gm. The epicardium in general was pale, smooth and glistening, except for two so-called "soldier's patches" measuring 2.5 by 3



Fig. 2.—Left ventricle opened showing location of microscope sections.

cm., one on the anterior and the other on the posterior surface of the right ventricle. The coronary arteries were straight and soft. On section, the myocardium was brownish red and no gross scarring was present. The right auricle was somewhat dilated and the pectinate muscles were hypertrophic. The endocardium was pale, smooth and glistening. The tricuspid leaflets and their chordae tendineae were not abnormal. The papillary muscles and trabeculae carneae were hypertrophied. The pulmonic leaflets were not abnormal. The left auricle was dilated, and the endocardium was slightly thickened and wrinkled. The mitral leaflets were irregularly thickened, particularly along the line of closure. At the base of the largest leaflet there was a thickened, irregular, calcified nodule, extending into the inter-

ventricular septum and through this to the base of the tricuspid leaflets. The chordae tendineae were slightly thickened but not fused or shortened. The papillary muscles and trabeculae carneae were somewhat hypertrophied. The endocardium of the interventricular septum showed several areas of opaque thickening. The pars membranosa of the interventricular septum was translucent and vascularized, and in the myocardium adjacent to it there was a small calcareous nodule 3 mm. in diameter.

The aortic leaflets were irregularly thickened and the free borders were rolled outward. There were numerous calcareous nodules present. The sinuses of Valsalva contain numerous elevated, firm nodular plaques. Surrounding the aortic ring were numerous yellow calcified plaques from 1 to 10 mm. in diameter. The orifice of the right coronary was slightly narrowed. The coronaries were patent and their intima was irregularly thickened by small yellow elevated plaques averaging 3 mm. in diameter.

Microscopic Sections: (See Fig. 2, for location of cut sections.)

Section 1. Interventricular septum adjacent to pars membranacea: The endocardium on the side of the left ventricle was moderately thickened by fibrous tissue and at the thinnest portion of the section there was marked thickening with numerous areas of calcification. The superficial layer of muscle was replaced by fibrous tissue, which extended to a slight degree between the adjacent muscle fibers. Midway between the two ventricular surfaces there was moderate replacement of muscle fibers by a dense, relatively acellular, connective tissue. In the endocardium on the side of the right ventricle there was a small area of fibrous thickening. The vessels in this region revealed a moderate thickening and hyalinization of all three coats, which was more pronounced in the medium-sized vessels. They were surrounded by an increased amount of fibrous tissue. The remaining portion of the section showed occasional small areas of interstitial fibrosis. The muscle fibers were of average size with well-preserved cross striation. The majority of the nuclei were small and found close together. An occasional large nucleus with square ends was seen. No Purkinje fibers were present in this section.

Section 2. Interventricular septum 4 cm. below aortic ring. The endocardium was moderately thickened by a loosely arranged, relatively acellular connective tissue, in which were large cells cut in cross-section. These showed a superficial resemblance to myocardial cells but were larger and contained a greater proportion of cytoplasm, the nuclei were small and irregular in shape and there was a tendency toward peripheral arrangement of the contracted fibrillae. The vessels and myocardium elsewhere in this section were similar to those in Section 1.

Section 3. Pars Membranacea adjacent to Section 1: There were marked sub-endothelial fibrosis and large areas of calcification, chiefly on the side of the left ventricle. This fibrosis extended deeply between the fibers of the myocardium. In many places the muscle fibers were small, palely stained and vacuolated. No Purkinje fibers were present in this section.

Section 4. Wall of left ventricle and left descending coronary artery: The epicardium and subepicardial fat showed no abnormalities. The intima of the coronary vessel was moderately thickened by fibrous change. The adventitia was thickened by hyalinized fibrous tissue. The myocardium contained numerous irregular areas in which the muscle cells had been replaced by dense connective tissue. The muscle fibers were large and had well-preserved striations and large nuclei, many of which had squared ends. Brown pigment granules were frequently present in the cytoplasm near the nuclei. The small coronary vessels showed a moderate degree of fibrosis. The endocardium was slightly thickened by acellular fibrous tissue.

Section 5. Posterior papillary muscle. There was a slight degree of acellular fibrosis throughout. The large coronary vessels showed marked thickening of the

intima by hyalinized connective tissue, and the adventitia was surrounded by an increased amount of dense, slightly cellular connective tissue. There was slight intimal fibrosis of the smallest vessels. The endocardium was moderately thickened by acellular fibrous tissue. The myocardium in this section was the same as in previous sections.

Section 6. Base of heart including left ventricle, left auricle, left circumflex artery and base of mitral valve: The intima of the coronary artery was considerably thickened by fibrous and hyalinized fibrous tissue. In the deep layers of the intima an occasional small capillary was present, and there was a slight infiltration of lymphocytes and an occasional polymorphonuclear leucocyte. The base of the mitral leaflet contained an increased amount of acellular hyalinized connective tissue. The endocardium of the left auricle was moderately thickened by acellular fibrous tissue. Myocardium was similar to that described above.

Section 7. Left ventricle taken parallel to surface and 3.5 cm. from apex: There is a slight degree of interstitial, acellular fibrosis, and moderate fibrosis of the small coronary vessels.

Note: No Aschoff bodies were present in the myocardium in any of the sections.

Aorta: The aorta measured 9.5 cm. in circumference at the arch. Extending throughout the aorta, particularly in the lower portion, there were yellowish gray, elevated plaques projecting above the cut surface. These were calcified in the region of the bifurcation. Microscopically there was marked intimal thickening by hyalinized connective tissue. The media showed a moderate degree of fibrosis. In the adventitia the vessels were slightly thickened and no cellular infiltration was present.

Femoral Artery: The vessel was markedly and irregularly thickened and calcified, particularly in the media. The size of the lumen was reduced by more than half. Microscopically there was extreme fibrosis and calcification of the media and marked irregular thickening of the intima by fibrous and hyalinized fibrous tissue.

Pathological changes of the other organs include a bilateral bronchopneumonia, pulmonary emphysema, arterial and arteriolar nephrosclerosis, and chronic cholecystitis with cholelithiasis.

DISCUSSION

This case of Stokes-Adams disease is one of the first reported as being successfully treated with ephedrine. In 1923 Feil¹ and other workers^{4, 5} had reported the successful use of epinephrine in this disease, and because of the similarity of action of the two drugs we decided to try ephedrine in our case. In 1925 Miller³ had reported the use of ephedrine in a patient having heart-block without Stokes-Adams attacks. The drug was used subcutaneously in 100 mg. doses, and there followed an increase in both auricular and ventricular rates as shown by electrocardiograms. In 1927 Hollingsworth² reported a case of Stokes-Adams disease which showed absence of attacks after receiving 50 mg. of ephedrine by mouth daily. Polygrams of the case were published but no electrocardiograms were taken. These two case reports were the only ones found in the literature. Recently, Wood⁷ reported the use of the drug in Stokes-Adams attacks.

According to Karsner⁸ the most common cause of permanent A-V block is coronary disease with its narrowing of the vessels supplying

the junctional tissues. As the vessels narrow, the A-V bundle and node undergo extensive degeneration and fibrosis. While our patient showed marked arteriosclerosis of his peripheral vessels both clinically and at autopsy, the coronary vessels were not seriously involved.

Looking for other explanations for the changes in the bundle, such as rheumatism, syphilis, diphtheria, scarlet fever or toxic agents, we find a lack of sufficient clinical and pathological evidence to ascribe the cause of the changes to them. We must then assume that the coronary sclerosis was sufficient to account for these changes.

SUMMARY

Subsequent observations with necropsy findings are recorded in a case of complete heart-block whose attacks of Stokes-Adams syndrome with periods of ventricular standstill were previously reported as having been controlled with ephedrine.

REFERENCES

1. Feil, Harold: The Use of Epinephrine in the Stokes-Adams Syndrome, J. A. M. A. 80: 26, 1923.
2. Hollingsworth, M.: Ephedrine in Adams-Stokes Syndrome, Calif. & West. Med. 26: 802, 1927.
3. Miller, T. G.: Clinical Value of Ephedrine, With Report on Its Effects in Certain Special Cases, Am. J. M. Sc. 157: 181, 1925.
4. Phear, A. G., and Parkinson, J. W.: Adrenalin in Adams-Stokes Syndrome, Lancet 1: 933, 1922.
5. Parkinson, J., and Bain, C. W. C.: The Adrenalin Treatment of Stokes-Adams Attacks, Lancet 2: 311, 1924.
6. Stecher, R. M.: A Note on Stokes-Adams Disease Treated With Ephedrine, AM. HEART J. 3: 567, 1928.
7. Wood, J. E.: Ephedrine in Adams-Stokes Syndrome, J. A. M. A. 98: 1364, 1932.
8. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott & Co.

CONGENITAL HEART-BLOCK

A CASE WITH OTHER CARDIAC ANOMALIES IN A STUDENT OF TWENTY-ONE YEARS*†

L. MINOR BLACKFORD, M.D., AND HENRY M. McGEHEE, M.D.
ATLANTA, GA.

ALTHOUGH heart-block is a grave omen, it does not of itself mean an early death. Taussig¹ has made the diagnosis in a woman of seventy-two years, whose pulse had been slow all her life, and who died of pneumonia four years later without signs of congestive failure. Hyman² has reported complete heart-block in an active, healthy man of fifty-eight years, whose pulse had been slow since the age of twelve years, "if not before." Pace³ has recorded another asymptomatic case with bradycardia of thirty-four years' known duration. White⁴ has under observation a woman, now forty-two years old and a champion golfer, with proved heart-block of fourteen years' standing. Death from heart failure in cases of block is due to failure of the myocardium.

Forty-four cases of congenital heart-block (complete in thirty-five) have just been reviewed by Yater, Lyon and McNabb.⁵ In six cases the heart was apparently normal except for the dissociation. In the majority, however, the clinical diagnosis was patent interventricular septum, and this defect was present in the five that came to necropsy. The atrioventricular bundle studied microscopically in three was imperfectly developed. Three other clinical cases of complete heart-block have been reported, two by Ellis⁶ and one by Wood and Roger.⁷ Prenatal bradycardia was noted in only one of the forty-seven.

When heart-block is discovered after the age of twenty years, it is difficult to be sure that it antedated birth. Diphtheria is thought by some not to cause permanent block. If this be so, when a patient with heart-block who has never had rheumatic fever states that his slow pulse was first observed in youth, it is reasonable to assume that the dissociation is congenital; only a previous normal electrocardiogram can prove the contrary. Therefore the heart-block in the patients of Taussig, Hyman, Pace and White (aged seventy-six, fifty-eight, forty-eight and forty-two years respectively) was probably of congenital origin, and three of these authors inclined to this opinion.

REPORT OF CASE

In the course of routine examination of the students at the Georgia School of Technology, September, 1931, interest was attracted by the slow pulse and the cordine manner of R. H., a slender, fairly well developed boy of nineteen years. He

*From the Emory University School of Medicine.

†The patient was presented before the Fulton County Medical Society on April 29, 1932.

stated that his pulse had always been slow. A tentative diagnosis of congenital heart-block with patent interventricular septum was made.

Mr. H., the boy's father, said that he himself had always enjoyed good health and that he had not used alcohol before 1920; he was not related by blood to his wife. Mrs. H. had never been particularly strong, but she had given birth to a normal baby both before and after B. In the summer of 1911 she was ill with malaria. Since she failed to rally satisfactorily, a laparotomy for suspected ovarian disease was advised. Operation revealed early pregnancy but no pathological condition. Before she came to term some months later, the family doctor noted that the fetal heart was slower than the maternal. After delivery B.'s pulse was

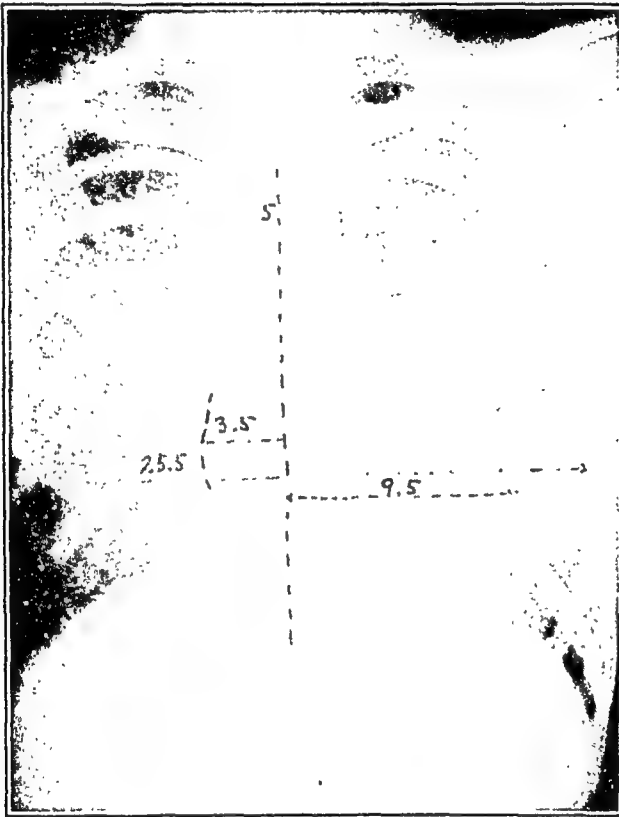


Fig. 1.—Anteroposterior teleroentgenogram. The silhouette suggests that of a guinea hen. It may be that torsion conceals hypertrophy of the right ventricle, which thus forms the apex. It may be that the hilar thickening is the result of hypertension in the pulmonary circulation. (Courtesy Dr. E. D. Shanks.)

still slower than his mother's. He was a blue baby. After a time the parents were told that he would "outgrow" his slow pulse, and they ceased to worry about it.

Except for repeated attacks of tonsillitis, B.'s childhood was essentially normal; cyanosis was not noted again and he experienced no dyspnea. Then frequent seizures of vertigo, and headaches with nausea and vomiting after unusual exertion began to annoy him. One hot day when he was nine years old, B. was sent to fetch a bucket of water and he fainted, remaining "limp for some ten minutes." A year later Dr. Albert E. Taussig reported, "The pulse was 44, rising only to 56 on violent exertion; the auricular rate was 109 as shown by the electrocardiogram, with complete auriculoventricular block." Though moderate restriction of activity was advised, the boy was encouraged to lead a normal life so far as the efficiency of his cardiovascular system would permit. The best criterion of this efficiency is

that B. fractured his left femur playing sandlot football in 1927. Headache and vomiting have recurred only once or twice since he first saw Dr. Taussig. He has never had any precordial pain or edema, but he has been taught to rest whenever tired.

Physical Examination.—There are no signs of edema, cyanosis or clubbing. Precordial bulging is marked: by actual measurement, the anteroposterior diameter of the left chest is from 1.5 to 2.0 cm. greater than that of the right. The apex beat is visible in the fifth interspace about 9 cm. from the midline, and retraction of the short ribs on the left synchronous with the heart beat can be seen behind. The left border of cardiac dullness extends 10 cm. in the fourth and fifth interspaces, and 7.5 cm. in the third. There is no increase in dullness to the right. A short, faint systolic murmur is heard at the apex and a long diastolic murmur to the left

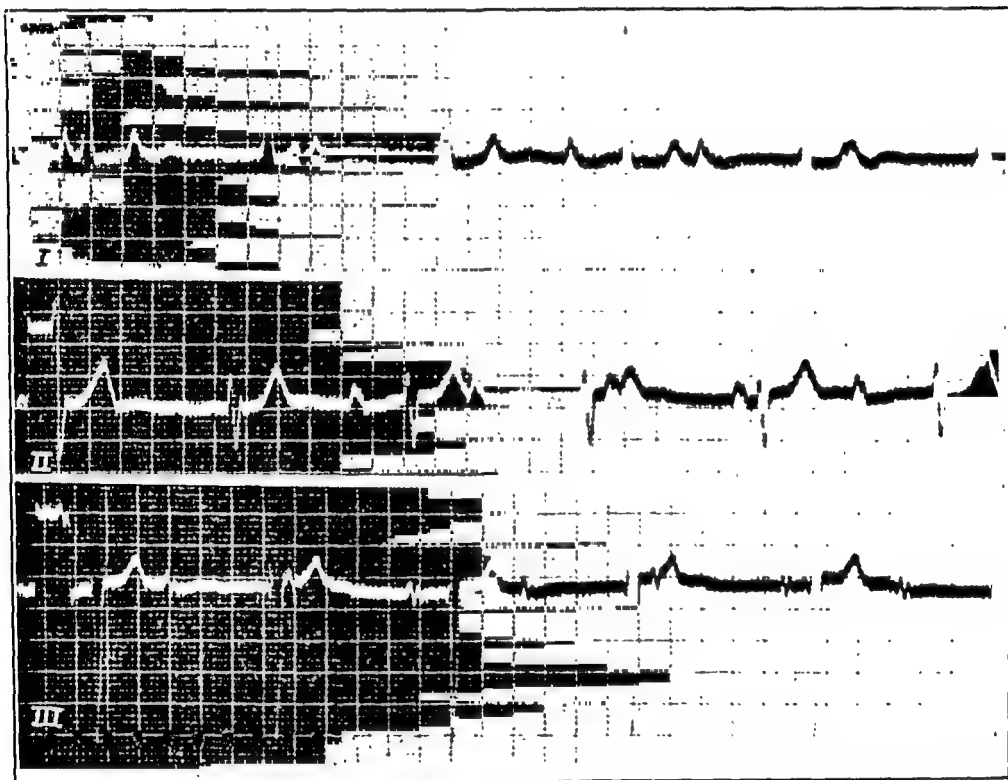


Fig. 2.—Electrocardiogram taken March 10, 1933. Auricular rate 66, ventricular rate 54: complete dissociation. (Courtesy Dr. E. D. Shanks.)

of the sternum, perhaps loudest about the third interspace, is present. The pulmonic second sound is accentuated: it is sharp and distinct several centimeters from midline. The pulse is of the "collapsing" type and there is a marked "pistol shot" in the groin. The pulse rate is 51 per minute. The systolic blood pressure is 110 mm.; there is a change in the character of the sound at 40, but it does not fade out until the mercury reaches 10 mm. Physical examination otherwise and routine laboratory tests are without interest. The anteroposterior teleroentgenogram is reproduced in Fig. 1; diagonal views with the esophagus visualized show that the left atrium is not enlarged, but indicate that the left ventricle is. One of the many electrocardiograms, all of which showed complete block, is shown in Fig. 2.

Epinephrin (0.5 c.c.) was administered. During the height of the reaction, which came after the electrocardiograph had been disconnected, 44 contractions (including four extrasystoles) to the half minute were heard at the apex.

DISCUSSION

The prenatal bradycardia, the immediate postnatal observations, the repeated records of slow pulse during infancy and childhood, the dramatic syncope at the age of nine years, the graphic evidence of heart-block at ten years, the absence of syphilis, diphtheria and rheumatic fever, all indicate that this heart-block is of congenital origin.

Although Abbott has emphasized that an accurate diagnosis of cardiac anomalies is often possible in an adult, a satisfactory one cannot be made in this case. Roentgenological studies often aid in the differential diagnosis, but they fail here because no similar one in a case that came to necropsy has been found. We believe that there is a lesion in the vital region of the membranous interventricular septum, which probably involves the right aortic leaflet, thus producing incompetence of the valve. This valve may be bicuspid. Intrinsic maldevelopment of the conduction bundle is almost certainly present.

Of greater clinical importance than the exact anatomical diagnosis, however, is the efficiency of the heart. Although this is hampered in B.'s case by the associated anomalies, which make strenuous forms of exercise inadvisable if not impossible, he has functionally a much better heart than ever had the noted musician reported by White and Sprague,⁸ who died of a cerebral accident in his sixtieth year. It is therefore entirely possible that B. may round out a successful career in his chosen profession. He is fortunate in having the means to secure a good education and in having been able to become well adjusted to his limitations. He is more than fortunate in having first consulted a wise physician who did not limit his activities more than was necessary, nor precipitate a disabling cardiac neurosis. Now that he has passed through adolescence, I am satisfied that the danger of heart failure is remote.

SUMMARY

In cases of congenital heart-block the prognosis depends largely upon the extent to which the anomalies which are usually concomitant limit the functional capacity of the heart. If these permit the subject to survive the early years, his future depends principally upon the intelligence of himself and of his physician.

Complete heart-block of congenital origin with structural anomalies in the case of a college student, now twenty-one years old, is reported. Bradycardia was first noted before birth. Although his physical activities are moderately limited, he may live another fifty years. Early heart failure is not to be expected.

REFERENCES

1. Taussig, A. E.: Personal communication.
2. Hyman, H. T.: Asymptomatic Heart-Block of Long Duration, *J. A. M. A.* 94: 27, 1930.

3. Pace, D.: Blocco completo del cuore che dura 34 anni, *Rinasc. med.* 7: 219, 1930.
4. White, P. D.: Optimism in the Treatment of Cardiovascular Disease; Case Reports, *Memphis M. J.* 9: 141, 1932.
5. Yater, W. M., Lyon, J. A., and McNabb, P. E.: Congenital Heart-Block: Review and Report of the Second Case of Complete Heart-Block Studied by Serial Sections Through the Conduction System, *J. A. M. A.* 100: 1831, 1933.
6. Ellis, L. B.: Clinical Studies in Complete Heart-Block; II. A Clinical Analysis of 43 Cases, *Am. J. M. Sc.* 183: 225, 1932.
7. Wood, W. A., and Roger, H.: Congenital Heart-Block: Report of Case, *California & West. Med.* 36: 397, 1932.
8. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot: Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, *J. A. M. A.* 92: 787, 1929.

Society Transactions

AMERICAN HEART ASSOCIATION, 1933

THE ninth annual scientific session of the American Heart Association was held at the Knickerbocker Hotel, Milwaukee, Wis., on June 13, 1933, with Dr. Walter W. Hamburger as presiding officer.

Program

Introduction. Walter W. Hamburger, M.D., Chicago, Ill.

Cytological Studies of Granulomata and Exudates From Patients With Rheumatic Fever. Currier McEwen, M.D., New York, N. Y.

ABSTRACT

Work previously reported has shown that rheumatic granulomata, as exemplified by the subcutaneous nodules, contain as their outstanding cytologic components, large cells having a characteristic appearance when exposed to neutral red and Janus green by the supravital technique. These cells differ in their reaction to these dyes from the characteristic cells of tuberculous and experimental syphilitic lesions. Essentially similar cells have been found in a further study of subcutaneous nodules from 7 patients with typical rheumatoid arthritis. They were not found, however, in examinations of 63 samples of joint exudate, 8 of pleural exudate, and 4 of pericardial exudate from 33 patients with rheumatic fever; or in 27 similar exudates from patients with other diseases. There was nothing characteristic in the joint exudates examined which served to differentiate those from patients with rheumatic fever. In the latter polymorphonuclear leucocytes predominated in most samples but tended to decrease in proportion to the clasmatoocytes as the joints recovered. Clasmatoocytes were also proportionately more numerous in exudates from patients over thirty years of age. From 3 to 20 per cent of lymphocytes and monocytes were present in most samples. The cells of pleural and pericardial exudates from patients with rheumatic fever were approximately the same as those of joint exudates save that 2 to 14 per cent of serosal cells were found in every sample.

The Importance of Allergy in Rheumatism. Edwin P. Jordan, M.D., Chicago, Ill.

ABSTRACT

There are numerous recent references to rheumatic fever as a manifestation of allergy. The evidence in favor of this hypothesis is based mainly on analogy, since the reproduction of rheumatic fever in experimental animals has not been successful. It was the purpose of the present work to determine whether joint lesions similar in character to those occurring in human joint disease and to those resulting from experimental allergic inflammation could be produced by nonprotein containing irritants. For this purpose turpentine and xylol were used. One c.c. of turpentine was injected directly into the right knee joint cavities of rabbits, and a similar amount of xylol into the opposite knee. The animals were sacrificed at varying periods of time following the injections and the synovia and the surrounding joint structures examined. In rheumatic fever in man the primary lesion of the joint appears to be synovial. In the experimental animals used the pathological changes

in the synovia can be traced through various acute stages to chronic or healing stages. From this work it appears that synovitis produced in rabbits by chemical irritants is not essentially different from that produced by the allergic inflammation observed by others. It is therefore not safe, in the present state of our knowledge, to draw etiological conclusions in rheumatic fever from the similarity of pathological changes produced in the joints of experimental animals by allergic inflammation.

Studies on the Etiology of Rheumatic Fever. T. Duckett Jones, M.D., and Josephine McBroom, A. B., Boston, Mass.

ABSTRACT

The etiology of rheumatic fever remains obscure despite much attention and extensive study of the disease during recent years. The evaluation of the rôle of the streptococcus, and more particularly of the hemolytic streptococcus, is discussed, especially in relation to throat culture work in rheumatic fever. Immunological reactions have not yet definitely proved any specific hemolytic streptococcus activity in rheumatic fever. Throat cultures have been made on 245 patients over a period of three and one-half years. The frequency of respiratory infection in this group is given, as well as the frequency with which hemolytic streptococci appear in the throat during the respiratory infection which precedes rheumatic fever. The close clinical relationship is noted. However, a close clinical relationship alone is not sufficient proof that the hemolytic streptococcus is the etiological agent in rheumatic fever.

Bacteriological Study of Throats in Rheumatic and Nonrheumatic Fever Cases With Special Reference to Hemolytic Streptococci. Israel Weinstein, M.D., and Norma C. Styron, A.M., New York, N. Y.

ABSTRACT

The investigation included 321 cases and 840 cultures taken from Montefiore and Bellevue Hospitals, New York City. Forty-six per cent of the cases were rheumatic fever patients. Fifty-eight per cent of the cultures were from this group. The remainder were from normal persons and those suffering from diseases other than rheumatic fever.

The results showed that hemolytic streptococci occurred no more frequently in the throats of rheumatic fever patients than they did in the throats of other individuals. During an upper respiratory infection the percentage of cultures showing hemolytic streptococci was no greater in the case of rheumatic fever patients than in other groups. However, young rheumatic fever patients suffering from an upper respiratory infection showed hemolytic streptococci in their throats more frequently than did older rheumatic patients. Those who had had their tonsils removed had these organisms less frequently associated with an upper respiratory infection than did those who retained their tonsils. In the groups studied, exacerbations of acute rheumatic fever occurred as frequently when there was no throat infection as when there was. The fact that the majority of those in whom exacerbations of rheumatic fever occurred were individuals having hemolytic streptococci in their throats suggests a possible relationship between this organism and the reappearance of the symptoms.

Dissociation of Streptococci Obtained From Acute Rheumatic Fever. Katharine M. Howell, M.D., and Eleanor P. Burton, A. B., Chicago, Ill.

• ABSTRACT

Strains of streptococci were obtained by blood culture from four patients during acute attacks of rheumatic fever. On blood agar, two strains were anhemolytic, one

slightly hemolyzing, and one greening. The anhemolytic strains grew in broth with uniform turbidity, the others with granular sediment. According to Holman's classification, based on sugar fermentations, the anhemolytic strains were *streptococcus salivarius*, the hemolytic, *streptococcus pyogenes*, and the viridans, *streptococcus mitis*. Three of the strains were highly virulent for white mice, the fourth (an anhemolytic strain) moderately virulent. Search for dissociation in these freshly isolated strains began with the original cultures and continued for months under various conditions. The original colonies from each strain were small, round, smooth, pyramidal, entire, and metallic. Films from all cultures revealed diplococci and short chains; bacillary forms, swollen cocci, and bizarre forms frequently occurred. Many types of media, chemicals, anaerobic conditions, animal passage, ageing, etc., were employed to induce dissociation. Unfavorable environmental conditions produced SR forms—granular consistency, roughened wavy edges, granular projections, and daughter colonies. Microscopically, marked pleomorphism was observed. These were the only indications of dissociation. Subcultures reverted to smooth types. Conclusion—the four freshly isolated strains of streptococci obtained by blood culture from acute rheumatic fever remained virulent, smooth and stable for five months. Elements of dissociation in the strains are suggested by pleomorphism and by occasional SR colonies. Prolonged cultivation with loss of virulence may induce dissociation.

Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children. Otto Saphir, M.D., and S. Wile, M.D., Chicago, Ill. See page 29.

A Clinical Conception of Rheumatic Heart Disease. Samuel A. Levine, M.D., Boston, Mass. See page 26.

Clinical and Pathological Study of One Hundred Cases of Mitral Disease. Charles S. Stone, M.D., and Harold Feil, M.D., Cleveland, Ohio. See page 53.

A Pathological Study of the Relationship of Auricular Fibrillation to Mitral Stenosis and Certain Rheumatic Tissue Changes. Clarence de la Chapelle, M.D., Irving Graef, M.D., and Antonio Rottino, M.D., New York, N. Y.

ABSTRACT

One hundred and eleven rheumatic hearts, obtained at necropsy in the past 13 years from the Third (N. Y. U.) Division of Bellevue Hospital, were examined. Forty-one were from patients who had established auricular fibrillation and 70 from patients who had sinus rhythm. The grade of stenosis was estimated as severe, moderate, or mild. Evidence of rheumatic inflammation was based on macroscopic examination in all and microscopic in 80. Blocks were taken after the method of Gross and Antopol. Of the 41 cases of fibrillation, 27 were over 40 years of age. Of the 70 cases of sinus rhythm, 28 were over 40. The grades of stenosis bore no relationship to the rhythm. Rheumatic inflammation was present in all cases of fibrillation under 40 years, and in only one-third of the cases over 40, independent of the grade of stenosis. This indicates that age may be a determining factor for the appearance of fibrillation in older subjects. In the sinus rhythm group, activity was present in 30 of the 42 cases under 40 years; and in 12 of the 28 cases over 40. Of the associated cardiac lesions, *tricuspid stenosis* occurred more frequently in the *fibrillation* group. Other lesions were uniformly distributed in both groups.

Paroxysmal Pulmonary Hemorrhages: The Syndrome in Young Adults With Mitral Stenosis. B. S. Oppenheimer, M.D., and Sidney P. Schwartz, M.D., New York, N. Y. See page 14.

Embolic Manifestations in Rheumatic Heart Disease. Soma Weiss, M.D., and David Davis, M.D., Boston, Mass. See page 45.

Electrocardiographic Findings in Experimental Pulmonary Embolism. John P. Anderson, M.D., Cleveland, Ohio.

ABSTRACT

An ante-mortem diagnosis of pulmonary embolism is comparatively rare while post-mortem diagnoses of this condition are comparatively common. There are three causes of emboli: (1) rheumatic hearts which develop intracardiac thrombi; (2) coronary thrombosis with mural thrombosis; (3) thrombosis or thrombophlebitis post-operative or otherwise in the peripheral venous circulation. One is sometimes at a loss to explain why a patient with rheumatic heart disease suddenly starts having more trouble than formerly or why the usual dosage of digitalis no longer seems to control the ventricular rate in cases with auricular fibrillation, or why patients suddenly develop acute attacks of pulmonary edema. Pulmonary embolism always has to be thought of in such cases. Similarly cases arise when a differential diagnosis has to be made between coronary thrombosis and pulmonary embolism, and two years ago a case arose which showed fairly characteristic electrocardiographic evidence of coronary thrombosis and that along with fever, leucocytosis, shock, reduced blood pressure, and a questionable friction rub made the diagnosis of coronary thrombosis seem fairly definite. At autopsy no evidence of coronary thrombosis was found and an extensive pulmonary thrombosis was apparently responsible for these signs. It was then decided to produce some pulmonary emboli experimentally and to observe the electrocardiographic changes produced. Several dogs were used and fairly consistent results obtained. These included tachycardia with disturbance of S-T segments with inverted T-waves. Coronary T-waves were encountered only once. The work will suggest a rather more rigid requirement for the electrocardiographic diagnosis of coronary thrombosis but whether the tracings are sufficiently differentiated to warrant electrocardiographic diagnoses of pulmonary embolism is uncertain. (Lantern slides showing serial electrocardiograms were demonstrated.)

The Heart in Rheumatic Fever and Rheumatoid (Infectious) Arthritis. Arthur M. Master, M.D., and Harry L. Jaffe, M.D., New York, N. Y.

ABSTRACT

This investigation continues a study* to distinguish between rheumatic fever and rheumatoid (infectious) arthritis. Daily electrocardiograms have now been taken on 63 patients suffering from acute rheumatic fever and on 46 patients with rheumatoid (infectious) arthritis. Evidence of myocardial damage was present in 100 per cent of the patients with rheumatic fever as evidenced by auricular fibrillation, auricular flutter, auriculo-ventricular conduction defect of more than 0.22 seconds, heart-block with dropped beats, RS-T changes, T-wave inversions in leads I and II. There were many abnormalities such as sino-auricular block, premature beats, nodal tachycardia, interference of sinus and A-V nodal rhythms. Not one of the 46 cases of rheumatoid (infectious) arthritis presented any of these abnormalities. In 5 cases the P-R interval reached 0.21 seconds, in one it measured 0.22 seconds. In 4 patients the T-waves were flat (iso-electric), once in lead I and thrice in lead III but not in a single instance was the T-wave inverted. In one patient there was a questionable reduction in voltage of the QRS group. Electrocardiographic evidence of myocardial involvement seems to be of real value in distinguishing rheumatic fever and acute rheumatoid (infectious) arthritis.

*Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever. J. A. M. A. 98: 881, 1932.

Lesions of the Kidney Associated With Rheumatic Heart Disease. Ann Purdy, M.D., San Francisco, Cal.

ABSTRACT

This article reviews briefly the literature in which kidney disease has been reported as occurring in the course of rheumatic heart disease. The author adds 2 cases of her own of hematuria in acute rheumatic fever in which the urine sediment did not return to normal in convalescence. No case is reported in which the kidney findings did not antedate salicylate therapy. This is followed by a survey of the heart and kidney findings in a selected group of cases seen in 3 cardiac clinics in San Francisco where rheumatic fever is said to be modified by climate. The cases were not selected alphabetically or chronologically; the families with "leads" were surveyed first. The cross-section of the group is in process. Some of these cases are pedigreed rheumatics, some are early and the diagnosis is open to question. All were studied in their family groups. A group of tonsillitis cases is reported. This group has been retained in the cardiac clinics by reason of their having been seen in an acute tonsillitis, or its allied diseases, or because they give a convincing history of them. They are being periodically scrutinized for the alleged sequelae. The pathological findings in the kidneys of patients dying of rheumatic heart disease and the pathological findings in the hearts of patients dying of nephritis are given. The clinical data are put forward for what they are worth, claiming not completeness, but timeliness. This article does not concern itself with the bacteriological considerations of these diseases and makes no etiological claims.

Skin Lesions in Rheumatic Fever: Observations on the Predominating Signs of Active Rheumatic Fever During a Ward Epidemic. William Chester, M. D., and Sidney P. Schwartz, M.D., New York, N. Y.

ABSTRACT

Skin manifestations have not received the attention they deserve as signs of activity in rheumatic fever. In a ward epidemic of this disease observed at the Montefiore Hospital during the months of March to November, 1931, 10 of 21 children showed skin lesions as the predominating sign of a recurrence or exacerbation of rheumatic fever. These lesions were most prevalent during August and September of that year and they occurred in crops. They appeared mainly on the lateral surface of the legs and the extensor surface of the forearms. They were rarely seen on the anterior trunk of the body. The regions about the joints were seldom involved. Their color was bluish, they were not tender, and varied in size from a lemon seed to a hazelnut. Most often they appeared as maculo-papular purpuric spots and persisted for from 1 to 6 months. In fading away very gradually, they underwent the pigmentary changes seen in subcutaneous hemorrhages with extravasation. No scarring or desquamation was seen to follow their disappearance. A total of 22 crops of skin lesions were studied in these 10 children. In 19 instances, an increased heart rate was an accompanying sign. Fever was present in a mild form on 13 occasions. Joint and muscle pains, choreiform movements, epistaxis, and congestive heart failure were each present in 2 instances. Hematological studies showed a persistent secondary anemia in all cases, a leucopenia and a positive Shilling count in 2 cases, and a transient thrombocytopenia and a positive tourniquet test in only one case. In one instance the P-R interval was prolonged. The appearance of skin lesions in children who have already had rheumatic fever should be considered as much a sign of reactivity as any other criterion accepted to date.

Incidence and Clinical Notes of Rheumatic Heart Disease in Southern Florida. E. Sterling Nichol, M.D., Miami, Fla. See page 63.

Convalescent Care of Cardiac Children. Hugh McCulloch, M. D., St. Louis, Mo.**ABSTRACT**

When the course of rheumatic heart disease shows progressive improvement, the management of the patient must be adjusted to the changed conditions, so that further improvement is favored and any relapse is prevented. This management is always to be adjusted to the individual circumstances and only general indications can be discussed. Progress will be determined by: (1) the type of response shown by the patient during the attack of rheumatic fever and heart disease; (2) the severity of the cardiac injury; (3) the number of preceding attacks; (4) the age of the patient. Useful signs of progress are: gain in weight, steady heart rate and body temperature, and physical signs in the heart of improvement. Influence of seasonal tendency to recurrence. Discussion of institutional convalescent care and relationship of cardiac child to school.

The Course and Prognosis of Rheumatic Fever and Chorea. T. Duckett Jones, M.D., and Edward F. Bland, M.D., Boston, Mass.**ABSTRACT**

The House of the Good Samaritan, Boston, Massachusetts, has since 1921 devoted a large number of beds to the hospital care of patients with rheumatic fever and chorea. In 1930 with the organization of a Research Department, an attempt was begun to assemble complete records and careful follow-up studies on these patients. With the cooperation of the large general hospitals of Boston and the institution of 2 weekly Out-Patient Clinics at the House of the Good Samaritan, a large amount of data has been assembled. A group of 1000 consecutive cases has been analyzed in an attempt properly to evaluate the life cycle of rheumatic fever and the resultant heart disease. The brief analysis here presented concerns itself largely with the frequency of the signs and symptoms of the disease, the frequency of reinfections, the importance of respiratory infections in connection with the disease, the seasonal and annual incidence, and prognosis.

Discussion**Discussion of paper by Dr. McEwen.**

Dr. Arthur M. Master, New York, N. Y.—Are the refractive bodies in the cells or in the granules seen in the neutral red stain different in the subcutaneous nodule of rheumatic fever and rheumatoid (infectious) arthritis?

Dr. McEwen.—In the nodules studied there tended to be more of the spindle-shaped cells in those from patients with rheumatoid arthritis, and such nodules not infrequently contained cells showing refractive bodies of larger size than any seen in cells from rheumatic nodules.

The majority of cells, however, were essentially the same so that one would have been unable to say, from examinations of individual cells, which type of lesion they came from. None of the characteristic cells from either type of nodule contained bodies which stained with neutral red.

Discussion of paper by Dr. Jordan.

Dr. A. G. Young, Boston, Mass.—Dr. Jordan's paper and the microscopic sections he has just shown do not convince me that he has ruled out the possibility of an allergic reaction in rheumatism. His slides show the usual inflammatory reaction to a chemical irritant. This does not coincide with the findings made by Dr. McMahon and myself in tissues taken from rheumatic fever and infectious arthritis patients. In the early acute stage one finds a flaky fluid exudate in the joint cavity containing few cells whereas the periarticular tissue is the seat of an acute inflam-

matory edema. The membrane is swollen, thickened and covered with a delicate fibrinous coating. The villi are thickened and the capillaries are markedly affected. Microscopically one finds synovial cells forming a thickened somewhat palisade-like wall. There are minute foci of necrosis, bordered by degenerating cells. The villi are enlarged, the connective tissue is edematous and infiltrated with few polymorphonuclear leucocytes and lymphocytes. In the deeper surrounding connective tissue Aschoff bodies may be found. I realize the difficulty in showing the entire pathological picture by lantern slides, but from what I have seen and from what Dr. Jordan has described I cannot agree that he has reproduced the rheumatic fever type of joint reaction by his chemical irritants.

Dr. M. H. Dawson, New York, N. Y.—It is very interesting to learn that Dr. Jordan has been able to reproduce with nonprotein substances the same type of lesion which Klinge produced by serum injections in sensitized animals. However, there is a doubt in my mind as to whether the lesions produced by Klinge and by Dr. Jordan are the same as those which occur in rheumatic fever and rheumatoid arthritis. The type of reaction in the naturally occurring diseases possesses certain rather distinctive characteristics which I do not believe have as yet been produced experimentally.

Dr. Jordan.—I hope that I have made clear that these findings are not an argument against allergy as the cause of rheumatic fever. The fact that a chemical irritant can produce pathological changes so similar to human arthritis is, however, an indication that great conservatism should be used in arguing by analogy. The palisading which Dr. Young mentioned does not seem to be a characteristic feature either of human synovia in arthritis or of the chemical synovitis.

Discussion of paper by Drs. Jones and McBroom.

Dr. Jones.—All students of rheumatic fever heartily agree that the disease is a general one, and the concentration of attention on respiratory infection and throat cultures does not in any way indicate that I am unaware of this important feature. The careful study of a large control series would be very valuable. The frequency with which hemolytic streptococci are present in the throat in normal persons during respiratory infection has not been sufficiently well observed. It may be well to stress the fact that recurrences of rheumatic fever occur in the absence of preceding respiratory infection, and that recurrences may help us to evaluate possible etiological agents.

Discussion of paper by Drs. Howell and Burton.

Dr. M. H. Dawson, New York, N. Y.—In a recent study of bacterial dissociation of *Streptococcus hemolyticus* we have been able to obtain quite similar types of colony variants. In our experience there is always a close relationship between colonial morphology and the morphology of the individual organisms constituting the colony.

Discussion of paper by Drs. Saphir and Wile.

Dr. Wm. Thalhimer, Chicago, Ill.—In spite of the diversity of opinion about rheumatic fever there is one point on which all investigators will agree; the cause of this disease has not been unquestionably established. Studies of rheumatic fever in recent years have concerned themselves chiefly with two subjects: The origin, nature and significance of Aschoff bodies—and the possible etiological relationship of streptococci to this disease. Thayer, in one of the last articles he published, stated that "streptococci have not been proved to be the cause of rheumatic fever." No new or conclusive evidence has been brought forward since Thayer's article.

The conception of the streptococcal cause of this disease, as a matter of fact, is not new, dating back to Poynton and Paine, and even earlier. The ease with which these workers recovered streptococci in blood cultures (in one instance by culturing two drops of blood from the ear into a flask of broth) is in striking contrast to the difficulty more recent workers have had. Poynton and Paine also believed, as some still do today, that subacute bacterial endocarditis is a malignant form of rheumatic fever.

At present there are two schools. One believes that streptococci are the direct cause of the disease and of the pathological changes found. The other believes that the same, or similar streptococci first cause an allergic condition and later stimulate repeated allergic responses which constitute the disease rheumatic fever.

The first group have recovered slow growing green or indifferent streptococci from the blood of about 60 to 70 per cent of the febrile patients studied, and these positive blood culture results decreased rapidly with the decrease and disappearance of fever. Nevertheless, the control group of blood cultures were taken on afebrile patients with other diseases. Surely a control group must be chosen as carefully as the experimental group, and one worker has secured streptococci in a large percentage of blood cultures from febrile, non-rheumatic patients.*

It is not my purpose to give the impression that cultivating these streptococci is a simple, easy job. It requires infinite care and excellent bacteriological technic. But Reith and Squier,† with a similar technic have recovered streptococci from a not insignificant number of apparently healthy individuals, who were well enough to carry on hard manual work.

Today, the recovery of an organism from the blood of a patient is not sufficient evidence that this is the cause of the patient's disease. Other criteria must be satisfied, even more today than when Koch announced his postulates. If streptococci cause rheumatic fever, we would expect to find them in appreciable numbers in the acutely and severely damaged heart valves and myocardium in this disease. I have never been able to find them at all, and cannot believe that an occasional coccus or diplococcus found, and then only after most careful and extensive search, can have any real significance. In other mortal, and less mortal, streptococcal diseases there is no difficulty in demonstrating streptococci in large numbers in the lesions.

Those who propose the streptococcus allergic theory as the cause of rheumatic fever cannot be right if streptococci are present in the blood stream of these patients, since they have shown experimentally that streptococci introduced into the blood stream destroy the previously developed allergic condition. Also, they have not been able to terminate the allergic state in human beings; i.e., the disease, by the intravenous injections of streptococcus vaccines. They believe that rheumatic fever develops at times into subacute bacterial endocarditis and with this the allergic state changes to a condition of immunity. Since individuals with this last disease almost invariably die, they can only be considered immune in a sense different from the usually understood meaning of immunity. Also, the presence of agglutinins in the blood does not indicate immunity (resistance to disease) any more than does the presence of complement-fixing bodies. The allergic theorists claim that they have produced Aschoff bodies in animals by means of repeated shocks caused by streptococci. This is doubted by some of us and brings up the dangerous question of the specificity and origin of these peculiar and interesting human lesions.

*Since this discussion was presented an important article has appeared. May G. Wilson and Helen Edmond in the American Journal of Diseases of Children, page 1237, June, 1933, report the recovery of the same types of streptococci from blood cultures from children with rheumatic fever and from a control group either apparently normal or with non-rheumatic types of disease, the percentage of positive streptococcus blood cultures being about the same in each group.

†J. Infect. Dis. 51: 336-343, 1932.

I do not believe that these problems can be solved with our present knowledge and background. New methods or new material, or both, will be necessary. Some of us believe that Aschoff bodies have peculiar characteristics (which can be described and demonstrated) different from any experimental lesions which have been produced. Others believe the contrary and neither can be convinced of the opposite point of view. Manifestly, no progress can be made under these conditions.

The question of the specificity of Aschoff bodies for rheumatic fever is in the same situation. Since it is well known that attacks of rheumatic carditis can occur without any of the recognized signs of rheumatic fever, and therefore these attacks can even be subclinical and not recognized—the mere absence of a history of rheumatic fever does not prove that this disease did not afflict the patient. The association of Aschoff bodies with gross cardiac lesions recognized as those of rheumatic fever outweighs, in my opinion, the arguments for the non-specificity of these bodies.

The gross endocardial and cardiac lesions of rheumatic fever are so different from those of subacute bacterial endocarditis that it is difficult to believe that these two diseases can be causally related. Even if one believes that some of the microscopic endocardial lesions of the two "conditions" are similar, it seems to me that more than a similarity of inflammatory reactions is necessary to prove the same etiology for the two diseases. One illustration is sufficient; many causes of encephalitis are recognized, but the encephalitic lesions caused by the different agents are so similar that one cannot determine cause from examination of the lesions.

The nature of the onset of rheumatic fever, the recurrences, the holding on and never letting go of the disease rheumatic fever, the peculiar and characteristic nature of the gross and microscopic cardiac lesions, make me think that this disease is not bacterial in origin but that its causative agent is more likely to be virus or protozoal in nature. This conception is not new but it seems to me is worth reviving. Others have searched for a protozoan or virus cause of rheumatic fever without success and I also have made unsuccessful searches for unknown organisms in cardiac material from rheumatic fever. This is a difficult search but it still interests me and perhaps may interest some of you.

Dr. Emanuel Libman, New York, N. Y.—To my mind, Dr. Thalheimer has not chosen well in drawing a comparison between the non-hemolytic streptococci found in cases of rheumatic fever and the bacillus typhi-exanthematici, in connection with drawing conclusions as to the etiological significance of the streptococci. It is well known that there is much risk in drawing inferences from comparisons of the biological character of organisms and the immunological responses to them. In this particular instance the risk is much greater. The streptococci that have been found in the cases of rheumatic fever are also present in the blood of a great variety of other conditions. The bacillus typhi-exanthematici (a pure anaerobe) has been isolated only in cases of typhus fever. Similarly, complement-fixation reactions with this organism have never been demonstrated in the blood of any other diseases, whereas complement fixation against non-hemolytic streptococci is found in many other conditions and in rheumatic fever. Of interest also is the fact that the above mentioned bacillus was found by Olitsky in abundance in the intestinal contents of infected lice. That the organism has a definite relationship to the disease is evident, but its exact rôle is as yet undetermined. Much more could be added in this connection, but I have stated enough to indicate that the comparison which has been made is not of any definite aid to us.

I have not made this statement because I am convinced of the etiological significance of streptococci in rheumatic fever. On the other hand, I have always felt that there is no binding evidence of such a relationship. Many years ago, like some others, I pointed out that the etiological agent might not be one of the ordinary

bacteria—and perhaps not be in the bacterial group at all. It would take up too much time to discuss this subject fully. I have elsewhere taken it up and have shown that the non-hemolytic streptococci are ubiquitous and may invade the blood in practically any disease.

It has long been known that subacute bacterial endocarditis occurs mainly on the basis of valvular defects of rheumatic origin, commonly in congenital defects, much less often in connection with luetic or atherosclerotic lesions, and that occasionally an apparently normal valve is affected. Notwithstanding the great frequency of the infection in valvular defects of rheumatic origin there is no evidence that the two diseases have a similar etiology. Like Drs. Saphir and Wile, I believe that other factors, particularly of a mechanical kind, play a decisive rôle.

I long ago noted combinations of active subacute bacterial endocarditis and recent rheumatic infection. Fresh Aschoff bodies were found in cases of active subacute bacterial endocarditis, and they were also encountered in the myocardium in cases of old valvular defect in which histological examination showed only old fibrous and calcareous changes and no evidence of active rheumatic infection. Fresh Aschoff bodies may even be found in combination with subacute bacterial endocarditis in the bacteria-free stage.

In this connection the paper of Drs. Saphir and Wile is a striking contribution. As they say, these observations must be taken cognizance of, in connection with any immunological conceptions concerning rheumatic fever.

Not only may recent Aschoff bodies be found in cases of active subacute bacterial endocarditis, but even active rheumatic valvular involvement. Thus I have reported a case in which there were present active rheumatic endocarditis of the aortic cusps and the posterior mitral flap, and recent subacute bacterial endocarditis of the anterior flap. I have also observed the following combination: recent rheumatic endocarditis of the aortic cusps, subacute bacterial endocarditis of both mitral flaps, and recent rheumatic endocarditis of the left auricle, on top of part of which was implanted a fresh attack of subacute bacterial endocarditis.

In regard to the rôle of focal infections, especially tonsillar infection, some clarity may perhaps be obtained by reference to a hypothesis which I have been recently formulating. According to it—in brief—any toxic focus may cause hyperemia and edema in various tissues of the body, and particularly in those previously affected by any infection (or intoxication), or metabolic disturbance. According to this idea, an infected tonsil, for example, can cause an activation of joints previously affected by the rheumatic virus. It is perhaps in this way that we can explain at least some of the beneficial results as regards articular involvement, that have been attributed to tonsillectomy. It is also permissible to consider that a previously diseased valve (or even a normal one) may repeatedly react to toxic foci by hyperemia and swelling. In that way recurrences might be set up, and fibrosis eventually increased. Every attempt must be made to eradicate all toxic foci, apart from a consideration of their harboring the actual rheumatic agent.

There is evidence that valves may become the seat of acute or subacute bacterial endocarditis in more than one way. It is difficult to say definitely which comes into play more often, embolism of the valve or implantation from the general blood stream. It is not easy to conceive that the infection is brought about by separate organisms floating in the blood. Perhaps the studies of Bull may be applicable here. He found that when bacteria are injected into the circulation, agglutination precedes their destruction.

Dr. Arthur M. Master, New York, N. Y.—In a discussion of the time relation between the appearance of subacute bacterial endocarditis and the preceding attack of rheumatic fever there are cases in which subacute bacterial endocarditis suddenly appears during the course of an attack of acute rheumatic fever. A boy of 14 years and a young adult of 21 both were admitted to the hospital suffering from

active rheumatic fever with an acute polyarthritis; no petechiae were present, urine and blood cultures were negative. With the development of an aortic diastolic murmur a subacute bacterial endocarditis became evident,—petechiae appeared, red blood cells were found in the urine, splenic infarcts were noted, blood cultures were positive. Both patients died and the diagnosis of subacute bacterial endocarditis engrafted upon previous rheumatic lesions was substantiated in each case.

Dr. Currier McEwen, New York, N. Y.—It does not seem to me that the presence of Aschoff bodies in the hearts of children dying of bacterial endocarditis is sufficient, in itself, to disprove the theory that rheumatic lesions are produced in tissues hypersensitive to streptococci while those of bacterial endocarditis occur only in the presence of circulating antibodies; because in rabbits rendered hypersensitive to streptococci, circulating antibodies against the same microorganisms can be quite regularly demonstrated. It may still be true that, while the typical rheumatic response is based upon hypersensitivity and the typical lesions of bacterial endocarditis are associated with circulating antibodies, patients in transition from one state to the other may show lesions of both types. Of course, too, it is doubtful whether one can tell the age of Aschoff bodies in a given instance, so that when found in hearts of children dying of bacterial endocarditis, such Aschoff bodies may be merely evidence of recent rheumatic carditis.

Dr. Samuel A. Levine, Boston, Mass.—The finding of simultaneous evidence of rheumatic heart disease and subacute bacterial endocarditis in these cases does not militate entirely against the conception that there is some antagonism between the two states in adults. I believe that there is sufficient clinical evidence from a large series of cases of subacute bacterial endocarditis observed in adults to warrant the general conception that certain types of rheumatic heart disease are more and others are less likely to develop subacute bacterial endocarditis. It is rarely seen in patients who have had previous congestive failure or who have had auricular fibrillation. It occurs most commonly in those who are in fairly good health and who are comparatively free from rheumatism.

Dr. T. Duckett Jones, Boston, Mass.—I should like to call Dr. Wile's attention to the ideas of Dr. Ronald T. Grant of London, England. In a recent series of lectures on "The Pathology of Endocarditis" delivered in this country, Dr. Grant stressed the probable rôle of platelet thrombi on valve surfaces as offering a good nidus of growth for bacteria, and a logical forerunner of bacterial endocarditis. Should thrombi be present and not too well organized, a transient blood stream infection would be all that is necessary for the development of bacterial endocarditis. Experimental proof of this may be forthcoming. It offers a logical explanation for many clinical and pathological features.

Dr. Saphir.—In answer to the remark that allergy is a biologic phenomenon, very intricate and difficult to understand, and that it should not be ruled out too soon as the underlying factor of rheumatic fever, I should like to say that just because it is so intangible it should not too readily be used as an explanation of a disease such as rheumatic fever. We must maintain that at the present time the cause of rheumatic fever is not known. On the other hand, we do believe that the Aschoff body is a specific granuloma caused by the unknown virus of rheumatic fever. Nodules have been produced experimentally which some observers hold identical to Aschoff bodies. We must emphasize, however, that none of the published illustrations are typical of Aschoff bodies. Since we believe that Aschoff bodies have not been produced experimentally, we have no right to assume that we know the etiology of rheumatic fever. It might very well be that our findings substantiate Dr. Libman's theory that a streptococcus bacteremia may lower the resistance of

patients who have had a quiescent rheumatic infection, reactivate the rheumatic infection and hence explain the finding of recent Aschoff bodies in cases of subacute bacterial endocarditis.

Discussion of paper by Dr. Levine.

Dr. L. Lichtwitz, New York, N. Y.—The relationship of the endocrine make-up, i.e., the constitution, to rheumatic fever was recognized by the older generation of physicians, and is occasionally taken up in recent publications. The study of this question, however, has been almost entirely crowded out by the concentration of investigative work on the infectious side of the disease.

A mere reference to the incidence of chorea and of nodose rheumatism in the female sex, indicates the importance of the subject. But even apart from this easily recognizable endocrine relationship, there is a close connection between constitution and rheumatic fever, one of the striking facts being that the kind of rheumatic infection from which a person suffers is determined by the constitution.

From a broad clinical point of view, there are two kinds of rheumatic fever. The first is characterized by marked articular swellings, frequent cardiac involvement, rheumatic cutaneous changes, and alterations of the walls of the capillaries. There is but little tendency for the joints to become stiff, and anti-rheumatic medication has a marked influence. In the second type there is absence of joint swelling but a great tendency to stiffness, and absence of cardiac and cutaneous changes. This kind of rheumatic fever is resistant to anti-rheumatics. The first form is encountered in young people with a thyroïdal constitution, and the second, in individuals of pyknic constitution.

Now the place of attack of every anti-rheumatic (analgesic, anti-pyretic) is the midbrain. It is certain that the hyperpyrexial form of rheumatic fever is a cerebral condition, with especial evidences of affection of the midbrain. The sweating of rheumatic fever, that occurs independently of use of medication, also signifies an involvement of the midbrain, just as oily skin and sweating do in epidemic encephalitis.

The midbrain is the most important regulator of every vegetative function—it is the most reactive and vulnerable part of the whole body. Fever and other phenomena of infection are evidences of this reactivity. Fever is significant of a regulating and defensive mechanism of the whole organism, just as local allergic or inflammatory phenomena are for a part of it.

We have been influencing the relationship and dependence of allergic reactions (of different kinds and degrees) to the midbrain and the neuroendocrine pattern—a question which is also of therapeutic importance.

Dr. B. S. Oppenheimer, New York, N. Y.—We have noticed a more than accidental association of rheumatic endocarditis, and also choreiform movements, and Graves' disease. The choreiform movements were much more marked than the gross muscular tremor or the exaggerated skeletal muscular movements which are observed at times in active Graves' disease. There appears to be some relation between Graves' disease, which manifests symptoms of endocrine disturbance, and the rheumatic group. The mechanism is not clearly established, but experience with instances of neurogenic Graves' disease has directed our attention to the sympathetic centers in the brain, and suggests that the common factor in the choreiform manifestations and Graves' disease may be found in the diencephalic centers which have just been discussed by Dr. Lichtwitz.

Dr. Emanuel Libman, New York, N. Y.—The subject introduced by Dr. Levine is surely one of real importance and interest. Some years ago I drew attention to

the apparent relationship of rheumatic fever and so-called status lymphaticus. A point worth following up is an apparent tendency for the occurrence of warts on the back of large flat hands of certain male adolescents having or developing aortic insufficiency.

Some years ago a rather elaborate paper was published in the *Wiener Archiv für Klinische Medizin*, by Hammerschlag, dealing with the constitutional disposition to rheumatic fever. It is worthy of study for its suggestive content.

Discussion of papers by Drs. Stone and Feil; Drs. de La Chapelle, Graef and Rottino; and Drs. Oppenheimer and Schwartz.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to know the frequency with which hypertension was associated with mitral stenosis in the series of cases reported by Drs. Stone and Feil.

Dr. Emanuel Libman, New York, N. Y.—Hemoptysis in connection with cardiac disease needs much further study. Even a comparatively short study of the subject will make it clear that other factors apart from those of a mechanical nature must often play a rôle. In the course of a paper published in 1918 I went into this aspect of the subject. In four-fifths of cases of suspected infarction, for example, only pulmonary apoplexy was found at the post-mortem examination. I drew attention to the importance of studying any tendency to bleed in the patient, and showed that this tendency is greater in the presence of hepatic insufficiency due to tricuspid disease.

Duroziez in 1878 pointed out that epistaxis and hemoptysis may be part of rheumatic fever in itself. In 1875 he drew attention to hemoptysis in cardiac cases as a cause of menstrual irregularity. Peter made similar observations.

Of particular interest in the cases reported by Drs. Oppenheimer and Schwartz are the remarkable early symptoms of the attacks. It would be important to know whether they appeared in the first as well as in later attacks. If they appeared for the first time in later attacks they might be attributed to fright and fear. But if they occur in first attacks, we have here a clinical picture that, as far as I know, has hitherto not been reported.

Dr. Arthur M. Master, New York, N. Y.—The present authors and many others have recently given evidence that with good care a patient with severe rheumatic valvular disease will go through with pregnancy and labor. This good care usually consists of rest, rest in bed and avoidance of upper respiratory infection. However, although the cooperation between obstetrician and clinician will bring about these fine results it must not be forgotten that there may be a decided after effect on the mother. It is my impression that the more pregnancies the patient goes through the shorter is her life span. A clinical impression is not a scientific method, however, and we are gathering statistics on this subject. Definite conclusions can only be based on a larger series of cases than has been reported.

Dr. Oppenheimer.—I am obliged to Dr. Libman for calling attention to the work of Duroziez on hemoptysis and epistaxis. In our paper, it was not attempted to discuss the whole question of hemoptysis, which of course occurs in a great variety of conditions. There is as yet no consensus of opinion as to the mechanism of hemoptysis in these various pathological conditions; for example, the cause of bleeding in so-called essential hemoptysis and also in essential hypertension is not at all clear. We are calling attention to an exceptional group of cases of prolonged severe hemoptysis associated with mitral stenosis, with unusual psychogenetic symptoms. It will be necessary to look into the individual histories to see, as Dr. Libman has

suggested, whether the psychoneurotic symptoms occurred with the very first attack of hemoptysis, or whether the initial hemoptysis started an anxiety neurosis which accounted for the nervous symptoms which initiated or preceded subsequent attacks of bleeding.

Dr. Feil.—Our cases of mitral stenosis associated with pregnancy are too few in number to draw any sweeping conclusions concerning the effect of pregnancy on the duration of life. We do believe that pregnancy is well tolerated by the majority of patients with mitral stenosis.

Discussion of paper by Doctors Weiss and Davis.

Dr. Lewis A. Conner, New York, N. Y.—In connection with this interesting study of the embolic phenomena in rheumatic heart disease it is well to emphasize the need for prompt diagnosis and prompt operation in cases of embolism of the large arteries of the extremities and possibly also of the pulmonary artery and the mesenteric arteries. The saving of a limb or a life will often depend upon the degree of coordination existing between the physician and the surgeon and the promptness with which the operation of embolectomy is performed.

It is well known that the operation offers the best chance of success if done during the period of blanching which immediately follows the blocking of the artery and often lasts but a few hours. When time has been given for the formation of a thrombus distal to the embolus, the outlook is much less favorable. In cases of mitral stenosis with auricular fibrillation, which is the condition most likely to be associated with such large arterial emboli, this possibility should therefore be kept constantly in mind and everything possible done in advance to insure prompt action if that should become necessary.

Dr. Fred M. Smith, Iowa City, Iowa.—I should like to ask Dr. Weiss if he has observed any relationship between infection and embolic phenomena. In some of the cases that we have observed, embolic manifestations seemed to follow a recurrence of rheumatic infection.

Dr. James A. Lyon, Washington, D. C.—I have listened with much interest to Doctor Weiss's analysis of the group of autopsied cases having rheumatic heart disease with embolic occlusion. Recently in private practice I have seen two interesting cases of embolic occlusion of major arteries of the greater circulation, followed by coronary occlusion and death. An embolectomy was performed in each of the two cases.

The first case was that of a white man, twenty-eight years of age, a bank clerk by occupation, who had been under my observation for three years because of rheumatic heart disease, mitral regurgitation and stenosis, congestive failure, and chronic auricular fibrillation. While at work, the patient had a sudden attack of intense pain in both groins, causing him to fall suddenly to the floor in a state of collapse. A physician who was called diagnosed the attack as neuritis and arterial spasm. On the seventh day after this circulatory accident, the patient was seen by Dr. Philip O. Pelland, an orthopedic surgeon, who found an entire absence of circulation in both legs. The patient was then admitted to Garfield Hospital where I saw him in consultation. It was evident that the initial attack had been caused by a saddle thrombus at the bifurcation of the abdominal aorta, which later on became dislodged and divided, entering the common iliac arteries. The following day, eight days after the initial attack, an embolectomy was performed by Dr. Harry Kerr, staff surgeon. Circulation was re-established in both legs. Unfortunately, on the day following the operation and again a week later there were evidences of fresh arterial occlusions,

and both legs again became cyanosed and the femoral arteries pulseless. A second embolectomy was performed by Doctor Kerr. A clot seven centimeters in length was successfully removed from the right femoral artery, reestablishing the circulation, but the attempted removal of the clots from the left femoral was unsuccessful. The patient continued to have repeated embolic deposits in both femorals, and twenty-five days after the initial attack both legs were amputated above the knees. One week following the amputation, the patient suddenly died of coronary thrombosis. At autopsy the orifice of the right coronary artery was found completely occluded by a large thrombus.

In the second case the patient, a retired white man seventy-five years of age, had arteriosclerotic heart disease and angina pectoris, which had shown increasing severity for the past two years. He was under my observation for more than a year. His initial attack was accompanied by severe pain in the left forearm. I saw him approximately one hour after the circulatory accident and found that his arm from the upper third downwards was pulseless and cold. There was a distinct wax-like band encircling the arm about four or five centimeters above the elbow. Two hours after the onset of the attack the patient was taken to Garfield Hospital, where an embolectomy was performed by Doctor Kerr. Unfortunately, the patient suddenly died of coronary thrombosis before the circulation had been reestablished in his arm.

It is evident from the history of these two cases that an early diagnosis should be made and an immediate embolectomy should be performed in cases of arterial occlusion in the extremities to prevent the possibility of the development of gangrene. However, there is ever present the possibility, even after an embolectomy, of these patients dying of coronary occlusion.

Dr. Arthur M. Master, New York, N. Y.—The mortality following embolectomy is high. Although, as Dr. Conner has pointed out, this is in a large measure due to delay in performing the embolectomy operation there are times when conservative treatment is indicated. The surgeon should see the patient as promptly as possible. We have recently seen two patients, both women with mitral stenosis and auricular fibrillation, recover completely after embolism. In one case there was evidence of a saddle-shaped embolus at the bifurcation of the abdominal aorta and the patient's condition was so poor that the surgeon, Dr. Harold Neuhof, decided upon conservative treatment. In the other case the patient had an embolus to the right popliteal artery with resulting beginning gangrene of the toe tips, with absolute rest and dry heat she recovered completely.

Dr. G. Werley, El Paso, Texas.—Massage for the relief of arterial embolism is a valuable suggestion. This brings up the question of differential diagnosis. I had a case in point. A man aged 41 years, had mitral stenosis and for three years the heart had been fibrillating, when he suddenly suffered paralysis of his right leg. The leg was pale, cold, pulseless and quite painful, and general symptoms of shock were noted. The symptoms and signs pointed plainly to embolism and preparations were made for embolectomy. After about an hour faint pulsations appeared in the femoral artery, a distinct thrill was felt and sounds like those heard on taking blood pressure were heard. In a short time he was able to move his leg and next day he could walk about the room.

Two months later he died suddenly following what we thought was embolism at the base of the brain. Post mortem examination showed slight atheroma of the right iliac artery with some rugation of the intima. Microscopically the intima was detached from the subjacent tissues over a small area. There was softening of the pons due to complete thrombosis of the basilar artery. There was an ulcerated

atheromatous patch at the base of the median mitral leaflet, but no evidence of thrombi in the left auricle.

Before attempting embolectomy, the possibility of intermittent claudication or thrombosis should be considered.

Dr. Weiss.—Dr. Conner's remarks urging us to recognize embolic occlusions of arteries early and to instruct hospital interns for prompt action in calling in a surgical consultant are very important. It is also important that every hospital should have one or two surgeons specially trained in embolectomy. It is often not appreciated that, on the whole, the performance of the embolectomy over certain arteries of the extremities is a relatively simple operation. I also agree with those speakers who pointed out that not all the arterial emboli of the extremities lead necessarily to gangrene. In a certain number of instances, particularly if the occlusion is only partial and the rapid organization or recanalization of the embolus reopens the circulation, complete recovery follows. As mentioned in the paper, the degree of collateral circulation is also a determining factor.

As to the rôle of massage in case of embolism, I know nothing.

We have made a similar observation to that described by Dr. Fahr, namely, that at times in a patient who has suffered from auricular fibrillation for many years, without obvious reason an embolus develops, and following this at various time intervals a number of other emboli occur. While the occurrence of embolism in rheumatic heart disease, as well as in arteriosclerotic heart disease, is not rare, it is surprising how little these problems have been studied from the statistical and clinical points of view.

Discussion of papers by Dr. Anderson and Drs. Master and Jaffe.

Dr. Louis N. Katz, Chicago, Ill.—The report by Drs. Master and Jaffe emphasizes again the importance of the electrocardiogram in determining heart involvement in acute infectious diseases such as rheumatic fever. With the paucity of physical findings often present during the active stage of rheumatic fever the study of serial electrocardiograms should be of great assistance in determining the presence of heart involvement. While physicians have overemphasized the importance of the electrocardiogram in other conditions, they have erred in the opposite direction in acute infectious processes. The electrocardiogram is a very useful adjuvant in estimating the condition of the heart in rheumatic fever and should be employed oftener.

The idea presented by Dr. Anderson is an excellent one, but an examination of his records fails to prove his point. The electrocardiogram of the patient he showed is of the bundle-branch type and is therefore not specific for a recent coronary thrombosis, although it may very well be caused by such a process. The changes in the electrocardiogram in his animal experiments are slight and we have seen similar changes from day to day in the normal, unanesthetized animal. With the evidence at present available I fail to see that the electrocardiogram in pulmonary embolism resembles in any way the changes seen in recent coronary occlusion. I should like, therefore, to emphasize that in differentiating recent coronary occlusions from allied conditions, the electrocardiogram is one of the most useful fields of electrocardiology.

Dr. M. H. Dawson, New York, N. Y.—It is very useful from the clinical point of view to be able to distinguish rheumatic fever and rheumatoid arthritis so clearly. However one point should be mentioned, namely, that the average age of the rheumatic fever patients studied was ten years younger than the rheumatoid arthritis group. It is well known that the degree of cardiac involvement in rheumatic fever

varies with the age of onset of the disease. Before definite conclusions are drawn, I think it is important that the average ages of the two groups should be comparable.

Dr. Master.—My cases did not include children. The youngest patient was thirteen years of age. I do not know what the same kind of investigation in children would show. I must repeat, however, that in adults one type of acute polyarthritis shows definite evidence of cardiac involvement, the other practically none.

Discussion of paper by Dr. Nichol.

Dr. B. S. Oppenheimer, New York, N. Y.—The data on rheumatic heart disease in Miami presented by Dr. Nichol is valuable, especially to those of us in the North who send patients who have suffered from rheumatic fever to the South. It is one of the important functions of the American Heart Association to stimulate interest in collecting facts on the geographical distribution of heart disease. It is disappointing to learn that a few cases of rheumatic heart disease have originated in Florida itself, even if the percentage of such cases among natives is very low. As to convalescence, it is worth noting that something may be accomplished, but apparently only temporarily, by sending the cardiac children who live under poor hygienic conditions to convalescent homes in the suburbs. The Mary Zinn Home for convalescent cardiac children ran for about seven years, just outside New York City. During their prolonged stay there the children gained in weight and height, and many of them had a healthy color, but on returning to their homes in the poor quarters of New York, they had about as many recurrences as the children who merely went to cardiac clinics, but never had had the opportunity of staying at a convalescent home.

Dr. T. Duckett Jones, Boston, Mass.—It has been my good fortune to have been associated for the past three years with Dr. C. F. Roche of Miami Beach, Florida, in transporting children with rheumatic fever and rheumatic heart disease to the St. Francis Hospital at Miami Beach. These children on the whole have recovered more rapidly in southern Florida than in New England. However, there have been recurrences of rheumatic fever among the group in Florida. This has happened despite the seeming rarity of hemolytic streptococcus infections in that vicinity and among the group. Dr. Nichol's paper is a very interesting one. It would seem to me, however, that it would be wise to limit the term "native" to those children who have never been out of southern Florida and those who rarely come in contact with tourists. With the large number of tourists annually, a large portion of the native population must come in contact with the causative agent of rheumatic fever, whatever it might be.

Dr. Nichol.—I am glad that Dr. Jones showed some pictures depicting the changed appearance of some of the rheumatic heart children after their stay in Florida. The point worth emphasizing, apart from the effect on the patient, is the infrequency of rheumatic heart disease *originating* in Miami, although some cases undoubtedly do arise there.

Discussion of paper by Drs. Jones and Bland.

Dr. W. D. Stroud, Philadelphia, Pa.—This report by Drs. Jones and Bland of their observations upon children and adults with rheumatic fever in Boston, should prove most valuable. It is interesting to note that in a similar group of individuals suffering from rheumatic heart disease in Bristol, England, Carey Coombs found a mortality of 21.4 per cent, while Dr. Jones, I believe, reported a mortality of 21 per cent. We have gained the same impression as that expressed by Dr. Oppen-

heimer, that the majority of these children, while they are in our convalescent hospital, have improved quite rapidly but that upon returning to their home environment, they seem to develop reactivations of their rheumatic fever just as frequently as children who have not had the care which our hospital affords. Perhaps their reactivations are not as severe, however.

Dr. Hugh McCulloch, Saint Louis, Mo.—We have studied the subsequent course of cardiac children who have had convalescent care in an institution. The results of this study showed that when they were discharged home, many of them showed attacks of rheumatic manifestations that were as frequent, or more frequent, than a group of rheumatic cardiac children who were under observation in the out-patient department and who had not been admitted to the institution. Our impression in this study was that the attacks suffered by the institutional group were shorter and less severe than those occurring in the home care group. We felt the institutional group had benefited by the care given them and that they were better able to go through these recurring attacks. It was very obvious in the study that the follow-up care of the institutional group is extremely important; that without strict medical and social supervision of the child after his return home with regulation of his various activities, all the benefits of institutional care would be lost.

Dr. Jones.—I would agree that the average age of onset of any group of patients will vary considerably depending upon the average age of the group being studied. It might also be pointed out that a satisfactory history of onset of rheumatic fever is rarely obtained from a middle-aged rheumatic. The onset may be so mild as to be completely forgotten even should the patient have been cognizant of it at the time. I feel that at present we cannot tell just what rôle chorea plays in rheumatic fever, or whether all chorea is rheumatic fever. It is evident, however, that as a rule chorea is closely associated with rheumatic fever, and that it seems to occur in those patients who do well clinically. Chorea alone without a history of rheumatic fever manifestations and without laboratory evidence of infection, rarely develops clinically evident heart disease. Conversely, those patients having rheumatic fever and later chorea or exhibiting manifestations of both conditions simultaneously will remain free from clinical evidence of heart disease in a larger percentage than the group who develop rheumatic fever following chorea. At the present time we cannot completely dissociate rheumatic fever and chorea.

Department of Reviews and Abstracts

Critical Review

THE ORIGIN OF THE HEART'S "INTERNAL STIMULUS"*

C. H. McDONALD, M.D., AND A. C. McDONALD, M.D.

LITTLE ROCK, ARK.

THE heart of either a cold or a warm blooded animal is able to maintain strong, rhythmical beats for a long time after all nervous, vascular, and supportive connections between the heart and the rest of the animal's body have been severed provided the heart is perfused with a liquid containing certain inorganic salts in proper proportion. To explain this automaticity of the heart many theories have been advanced. Those based upon a more modern conception of physics and chemistry date from about 1870. Attention has been directed toward the various factors supposedly capable of calling out the heart beat—the so-called "inner stimulus"—in a somewhat cyclic manner: toward first the organic constituents, then the inorganic, next the possible physicochemical arrangements of both organic and inorganic, again toward the organic, and at the present time there is a renewed interest in the inorganic constituents with respect to their possible rôle in releasing the heart beat.

Langerdorf³⁰ advanced a theory that the inner stimulus controlling the automaticity of the heart arises from cleavage processes within the heart, probably in the ganglion cells—"Der Lebensprodukt der Zelle is ihr Erreger." This stimulus originates in the catabolism of the cells, and anabolic processes are assumed to diminish its production. Thus, adopting a view earlier expressed by Gaskell, the inhibitory nerves produce their effects by increasing the anabolic processes. Assuming a constant production of this stimulating substance, he explained the rhythmicity on Rosenthal's hypothesis of a steady stimulus opposed by a steady resistance. Langendorf placed the burden of calling out the heart's rhythmic beats upon the organic constituents of the heart and assigned to the inorganic cations, sodium, potassium, and calcium, the minor rôle of placing the cardiac musculature in proper condition for the action of the inner stimulus.

*From the Department of Physiology and Pharmacology, University of Arkansas School of Medicine.

Englemann,¹⁹ basing his views mainly upon a study of the automaticity of the venous end of the heart, believed that a stimulating substance responsible for the inner stimulus is formed as a result of the resting metabolism of the heart. The accumulation of this material during the pause suffices eventually to bring on a systolic contraction. The diastolic pause in its duration is the reciprocal of the rate of development of the stimulating substance. To explain the rhythmicity it is suggested that each systolic contraction causes a diminution or neutralization of the stimulating substance. These views of both Langendorf and Englemann are entirely theoretical inasmuch as nothing of the nature of direct proof is given for existence of such a stimulating substance in the heart.

Ringer⁴⁴ noted that if an excised heart is perfused with an aqueous solution of the salts of sodium, calcium, and potassium in the concentration in which these salts are found in the animal's blood, a rhythmical, functional beat may be obtained for a long time. He believed that no artificial perfusion fluid could so function unless it contained the salts of these cations and from this reasoned that an interaction of these inorganic salts is a necessary condition for the heart beat. He emphasized an antagonistic action of calcium and potassium upon the tone of the cardiac musculature and suggested that calcium elicits the contraction of the heart's tissues while potassium brings about their relaxation.

Loeb³³ observed that the presence of certain ions influences the imbibition of water by soaps and that variations of the kind and concentration of these ions within the soap can cause water to proceed into or out of the soap. He further noted that changing the kind and concentration of these same ions in the fluid bathing an excised skeletal muscle can vary the activities of this muscle. These observations led him to postulate a mechanism by which ionic activity serves to release the spontaneous, rhythmic contractions which can be called forth in skeletal muscle under certain conditions. He expressed the conviction that the same mechanism can be extended to cardiac musculature. According to Loeb's theory, the various ions exert their influence by entering the cell and uniting with certain cellular constituents. Acting as the principal agent in initiating automaticity, the sodium ion enters the cell and displaces a small portion of the calcium ion from its intracellular compounds and by this displacement excites the muscle to contract. If this displacement proceeds too far, the sodium ion "poisons" the tissue. In this theory of the origin of the heart's automaticity Lingle concurred.

Howell²⁵ advanced a theory in which an antagonism between sodium and calcium present in balanced ratio acts as the exciting agent for spontaneous beats rather than the activity of sodium alone as Loeb

believed. Howell denied the "poisoning" action of sodium upon cardiac tissue except so far as any single known substance is likewise poisonous in being unable to support rhythmic beats when used alone. Warburg⁴⁸ has recently shown, however, a so-called toxic action of sodium chloride upon certain cells in that their oxidations are greatly increased when sodium chloride is the only salt contained in the fluid surrounding them; furthermore, this increased oxidation is neutralized by the addition of calcium salts or of sodium cyanide to the fluid in contact with the cells. Loeb, Lingle, and Howell agree in assigning no direct action in the production of the inner stimulus to potassium. It should be borne in mind that rhythmicity at this time was defined wholly in terms of mechanical contractions.

Zwaardemaker,⁵⁰ however, placed the responsibility of initiating the heart's spontaneous rhythm upon potassium. While holding sodium, calcium, and potassium as essential to the maintenance of a rhythmic beat, he asserted that the radiations emanating from the potassium act directly upon the heart's musculature stimulating it to its rhythmic contractions. His modified view of the behavior of potassium will be noted in connection with the heart hormone theory. He held that potassium can be replaced in its effect by any other radioactive substance. He divided the radioactive substances into two groups dependent upon the nature of their emanations, soft alpha or hard beta rays, and asserted that the two groups are antagonistic to each other in their effects upon the heart. This specific rôle assigned to potassium in calling out the heart beat has been criticized by Clark¹⁰ and by Libbrecht,³¹ while Zeehuisen⁴⁹ has shown that failure of the heart's rhythmicity is not directly connected with the removal of potassium from the heart's tissues.

Mines³⁸ advanced an interesting and rather comprehensive physico-chemical theory to account for the origin of the heart beat. He assumes that the contractile mechanism responds to a transitory increase of hydrogen ions at interfaces within the cardiac muscle structure. Such a change in hydrogen ion concentration will be dependent upon the maintenance of a certain degree of permeability of the cell surfaces or cell membranes. Maintenance of this proper degree of permeability is a function both of the chemical composition of the cell membrane and of the electrical potential existing across the membrane itself. He has classed the calcium ion as a combining ion, capable of entering into chemical union with the membrane itself and exerting an influence upon its permeability. The sodium and potassium ions he has classed as nomadic ions because of their supposed ability to penetrate the cell membrane and by such migrations exert an influence upon the electrical charge of different parts of the cell. The hydrogen and hydroxyl ions he classes as polarizing ions which affect the

surface potential of the cell through adsorption. Hogben²⁴ has also furnished experimental evidence in confirmation of this view.

Clark⁹ has advocated a somewhat similar theory in which lipoids become essential constituents of the cell surfaces. The function of calcium is to vary the colloidal state of this lipid-containing cell surface. The permeability of the cell to electrolytes is made dependent on, or influenced by, the presence of calcium and lipoids at the cell surface. Clowes¹¹ has constructed a model in which both conductivity and permeability of a membrane soaked in an emulsion of oil and balanced soap solution vary with changes in the calcium to sodium and potassium ratio due to the degree of externalization of the lipid phase of the cell membranes. Osterhout⁴⁰ made a like observation with living plant tissues. Rona and Petow⁴⁵ explain the mutual antagonism of calcium and potassium upon the basis of opposed influences in the externalization of the lipid phase of cell membranes.

Andrus and Carter¹ have elaborated a physicochemical theory in which the hydrogen ion concentration in different parts of the cell explains the origin of the heart beat. The cardiac rhythm, according to these investigators, is due to the rhythmic building up and discharging of a potential difference across a semipermeable membrane. The rate of discharge and the magnitude of this potential difference are dependent fundamentally upon the difference in hydrogen ion concentration within the cardiac tissues and the fluid bathing them. The level of the potential difference at which this discharge takes place is determined by the permeability of the interposed membrane which is in turn dependent upon the concentration of the sodium, calcium, and potassium salts on either side of the membrane. Mention must be made of a belief that carbon dioxide acts as the internal stimulus itself. This view was first advanced by Martin³⁶ and has been elaborated by Mansfeld and Szent-Györgyi.³⁵

Lillie³² explains the heart's automaticity on the basis of alternation between states of activity and passivity perhaps of the nature of oxidation-reduction reactions. He has constructed inorganic models capable of exhibiting such phenomena as chronaxia, electrotonus, polar stimulation, inhibition, and refractory period in close agreement with living systems.

Zwaardemaker⁵¹ altered his original theory in which potassium by its radioactivity stimulates the heart tissue directly to one in which a hormone manufactured by the skeletal muscle is changed by the radioactivity of potassium to a substance (automatin) which is capable of imparting automaticity to the cardiac tissue. Haberlandt²³ has proposed a similar theory in which a hormone is formed constantly by the conducting tissues of the heart and is responsible for the cardiac contractions. He explains alternate contraction and relaxation as

a function of the refractory period of the heart cells. Demoor¹⁵ has advanced a somewhat different humoral theory. According to his view, the myocardium is capable of giving automatic contractions but the contractions are irregular. Under the influence of a substance elaborated particularly by the nodal tissue the myocardium assumes regularity. His theory is based chiefly upon the observation that the right auricle of the rabbit excised and dropped into a Ringer-Locke solution soon assumes a regular rhythm; the left auricle, however, gives only aperiodic, jerky beats in this solution. If now the solution in which the right auricle has been active for a while is poured over the left auricle, the latter assumes rhythmical beats. We have been able to confirm this observation in about 70 per cent of trials. (Preliminary publication, *Proc. Soc. Exper. Biol. & Med.* 30: 786, 1933.) Demoor has postulated other heart hormones which bring about augmentation and inhibition of the heart. The "specificity" of these substances has been questioned since extracts of other tissues have been shown to have similar effects upon the heart tissue. Asher and Beyeler,³ Granit and von Bonsdorff,²² Katz and Liebenson,²⁷ Rigler and Singer,⁴¹ Rigler and Tiemann,⁴² Oppenheimer,³⁰ Kraut, Frey, and Werle,²⁹ Thorpe,⁴⁷ Cannon and Griffith,⁷ and Chang and Chen⁸ have demonstrated that such substances have a wide distribution in the tissues.

With the development of instruments capable of measuring the electrical variations that occur in connection with the mechanical movements in contracting musculature there has been made available a new criterion for the presence or absence of contractions in a heart. It was long supposed that the electrical phenomena were concerned perhaps solely with the internal stimulus and definitely preceded any distortion of the muscle substance. Einthoven,¹⁷ Einthoven and Hügenholtz,¹⁸ Arbeiter,² and de Jongh¹⁴ have advanced the idea that electrical and mechanical phenomena are indissoluble; while Gasser and Hill,²¹ Rijlant,⁴³ Kleinknecht,²⁸ Fulton,²⁰ Jolles,²⁶ Bishop and Gilson,⁵ Max,³⁷ and Baetjer and McDonald⁴ have presented evidence that the two may be separated.

Without much speculation upon the actual origin of the electrical variation shown by the beating heart, Craib¹² has called into question the usual method of explaining this variation upon the basis of a state of negativity which is developed by acting tissue as compared to that of resting tissue. He offers mathematical and experimental proof that the electrical phenomena of the heart partake of the nature of what he terms "electrical doublets" and defines an electrical doublet as two closely adjacent poles situated within a conducting medium and maintained at equal and opposite potentials.

At any rate, since the electrical phenomena in connection with the heart's contraction may be used as a means of measuring the heart's

activity, the functional importance of the inorganic ions in the production of the internal stimulus has become a subject for reinvestigation. Briefly stated, it appears that according to the present view sodium is perhaps most intimately concerned with actual release of the internal stimulus, calcium with the strength of contraction, and potassium with the counteracting of an irritating antagonism between sodium and calcium. Reference may be made to Clark,¹⁰ Arbeiter,² Ten Cate,⁴⁶ Hogben,²⁴ McDonald,³⁴ Zeehuisen,⁴⁹ Colle,¹³ Bouckaert and Belehradek,⁶ Zwaardemaker,⁵¹ Max,³⁷ and Baetjer and McDonald.⁴

REFERENCES*

1. Andrus, E. C., and Carter, E. P.: Development and Propagation of Excitatory Process in Perfused Heart, *Heart* 11: 97, 1924; also *Science*, Nov. 9, p. 376, 1923.
2. Arbeiter, W. C. A.: Phenomena Mechanical and Electrical in the Frog Heart After Removal of the Calcium, *Arch. néerl. de physiol.* 5: 185, 1921.
3. Asher, L., and Beyeler, K.: *Biochem. Ztschr.* 178: 351, 1926.
4. Baetjer, A. M., and McDonald, C. H.: The Relation of the Sodium Potassium, and Calcium Ions to the Heart Rhythmicity, *Am. J. Physiol.* 99: 666, 1932.
5. Bishop, G. H., and Gilsen, A. H., Jr.: Action Potential Accompanying the Contractile Process in Skeletal Muscle, *J. Physiol.* 82: 478, 1927.
6. Bouckaert, J. P., and Belehradek, J.: Concentration des ions et contraction musculaire, *Arch. internat. de physiol.* 29: 71, 1927.
7. Cannon, W. B., and Griffith, F. R.: A Hormone Produced by Sympathetic Action on Smooth Muscle, *Am. J. Physiol.* 96: 392, 1931.
8. Chang, H. C., and Chen, Y. P.: *Chinese J. Physiol.* 5: 363, 1931.
9. Clark, A. J.: The Action of Ions and Lipoids Upon the Frog's Heart, *J. Physiol.* 47: 66, 1913.
10. Idem: The Mode of Action of Potassium Upon Isolated Organs, *J. Pharmacol. & Exper. Therapeut.* 18: 432, 1921.
11. Clowes, G. H. A.: The Action of Electrolytes in the Formation and Inversion of an Oil-Water System, *Kolloid-Ztschr.* 15: 123, 1914.
12. Craib, W. H.: A Study of the Electrical Field Surrounding Active Heart Muscle, *Heart* 14: 71, 1927.
13. Colle, J.: Ions and the Frog Heart, *Arch. internat. de physiol.* 29: 71, 1927.
14. de Jongh, C. L.: Der Zeitverhältnisse zwischen electromechanokardiogram, *Pflüger's Arch.* 213: 216, 1926.
15. Demoor, M. J.: Humoral Regulation of Heart Action of Active Substance From Region of Node in Right Auricle, *Compt. rend. Soc. de biol.* 91: 90, 1924; *Bull. Acad. roy. de méd. de Belgique*, Dec. 15, 1928; The Humoral Regulators in the Heart, *Ext. de la Presse Méd.* 60, du Juillet, 1929.
16. Idem, and Rylant, M. P.: *Arch. internat. de physiol.* 23: 121, 1924; *ibid.* 26: 113; *ibid.* 27: 1, 1926; Regulation by Body Fluids of Work of Heart Ventricle—Active Substance of Subendocardial Tissue, *Compt. rend. Soc. de biol.* 95: 219, 1926; Mech. of Action of Subendocardial Tissue in Ventricles, *ibid.* 95: 221, 1926.
17. Einthoven, W.: The Relation of Mechanical and Electrical Phenomena of Muscle Contraction With Special Reference to Cardiac Muscle, *The Harvey Lectures*, p. 111, 1924.
18. Idem, and Hügenholtz, F. W. N.: The Electrocardiogram Traced in the Case Where There Is No Visible Contractions of the Heart, *Arch. néerl. de physiol.* 5: 174, 1921.
19. Englemann, Th. W.: *Pflüger's Arch.* 65: 109, 1897.
20. Fulton, J. F.: The Influence of Tension Upon the Electrical Response of Muscle to Repetitive Stimuli, *Proc. Royal Soc. B* 97, 1925.

*A bibliography more than twice as extensive of the literature concerning this field may be had in McDonald, C. H.: The Relation of the Sodium, Potassium, and Calcium Ions to the Heart Rhythmicity, Welch Medical Library, Johns Hopkins University.

21. Gasser, H. A., and Hill, A. V.: The Dynamics of Muscular Contraction, *Proc. Royal Soc. B* 96: 398, 1924.
22. Granit, R., and von Bonsdorff, K.: *Skandinav. Arch. f. Physiol.* 5: 249, 1926.
23. Haberlandt, L.: Ueber ein Hormon der Herzbewegung, *Pflüger's Arch.* 220: 203, 1928.
24. Hogben, L. T.: Studies on the Comparative Physiology of Contractile Tissue, *Quart. J. Exper. Physiol.* 15: 263, 1925.
25. Howell, W. H.: An Analysis of the Influence of the Sodium, Potassium, and Calcium Salts of the Blood on the Automatic Contraction of Heart Muscle, *Am. J. Physiol.* 6: 181, 1901; Vagus Inhibition of the Heart in Its Relation to the Inorganic Salts of the Blood, *Am. J. Physiol.* 15: 280, 1906.
26. Jolles, W. H.: *Onderz. Physiol. Lab. Utrecht* 5: 18, 1927.
27. Katz, G. J., and Leibensohn, E. C.: Recherches sur les hormones cardiaques, *Compt. rend. Soc. de biol.* 99: 695, 1928; *Pflüger's Arch.* 221: 213, 1928.
28. Kleinknecht, F.: *Ztschr. f. Biol.* 81: 5, 1924.
29. Kraut, H., Frey, E. K., and Werle, E.: Der Nachweis eines Kreislaufhormons in der Pankreasdrüse, *Ztschr. f. Physiol. Chem.* 189: 97, 1930; Ueber die Inaktivierung des Kallekreins; über dieses Kreislaufhormon, *ibid.* 192: 1, 1930.
30. Langendorf, O.: Studien über Rhythmik und Automatic des Froschherzen, *Arch. f. Anat. u. Physiol.* 1: 137, 1884; *Ergebn. d. Physiol.* 2: 263, 1902; Ueber die angebliche Unfähigkeit des lackfarbrenen Blutes den Herzmuskel zu ernähren, *Pflüger's Arch.* 93: 286, 1903.
31. Libbrecht, W.: Contribution à l'étude du rôle biologique du potassium sur le cœur, *Arch. internat. de physiol.* 15: 446, 1927.
32. Lillie, R.: Analogies Between Physiological Rhythms and Rhythmical Reactions in Inorganic Systems, *Science J.* 15: 593, 1928.
33. Loeb, J.: *Festschr. f. Fick*, Braunschweig, p. 99, 1899; On Ion-Proteid Compounds and Their Role in the Mech. of Life Phenomena, *Am. J. Physiol.* 3: 327, 1900; *Pflüger's Arch.* 88: 68, 1901; Studies on the Physiological Effects of the Valency and Possibly the Electrical Charges of Ions, *Am. J. Physiol.* 6: 411, 1902.
34. McDonald, A. D.: Action of Adrenaline on the Perfused Fish Heart, *Quart. J. Exper. Physiol.* 15: 69, 1925.
35. Mansfeld, G., and Szent-Györgyi, A. V.: Untersuchungen über die Ursache des Herzschlages, *Pflüger's Arch.* 184: 236, 1920.
36. Martin, E. G.: On the Relation of the Inorganic Salts of Blood to the Automatic Activities of a Strip of Ventricular Muscle, *Am. J. Physiol.* 2: 82, 1904; A Study of the Absorption and Consumption of Oxygen in Heart Tissue, *ibid.* 15: 303, 1906; A Study of the Relations of the Inorganic Salts of the Blood to the Contraction of Heart Muscle and Skeletal Muscle, *ibid.* 16: 191, 1906.
37. Max, L. W.: Time Relations of Electrical and Mechanical Responses of Heart Muscle, *Am. J. Physiol.* 98: 318, 1931.
38. Mines, G. R.: Electrolytes on the Heart, *J. Physiol.* 43: 467, 1912; On Functional Analysis by the Action of Electrolytes, *ibid.* 46: 188, 1913.
39. Oppenheimer, E. T.: Studies on the So-called Heart Hormone, *Am. J. Physiol.* 90: 656, 1929.
40. Osterhout, W. J. V.: The Penetration of Balanced Solutions and the Theory of Antagonism, *Am. J. Botany* 9: 172, 1916.
41. Rigler, R., and Singer, R.: Ueber das Herzshormon, *Pflüger's Arch.* 220: 56, 1928.
42. Idem, and Tiemann, F.: Ueber den Herzautomaticstoff, *ibid.* 222: 450, 1929.
43. Rijlant, M. P.: Actual Methods of Studying the Automaticity and the Conduction in the Heart, *Bull. et Ann. de la Soc. Roy. de Sciences Méd. et Nat. de Bruxelles* No. 102, 1929.
44. Ringer, G.: Concerning the Influence of Each of the Constituents of Blood on the Contraction of the Ventricle, *J. Physiol.* 3: 380, 1883; *ibid.* 4: 370, 1883; On the Mutual Antagonism Between Lime and Potash Salts in Toxic Doses, *ibid.* 5: 247, 1884; Regarding the Influence of Organic Constituents of Blood on Contractility of the Heart, *ibid.* 6: 361, 1885.
45. Rona, P., and Petow, H.: Beitrag zur Frage der Ionenverteilung im Blutserum, *Biochem. Ztschr.* 137: 356, 1923.

46. Ten Cate, J.: L'action du sympathique et du vagus sur le coeur de grenouille, Arch. néerl. de physiol. 10: 544, 1925.
47. Thorpe, W. V.: The Isolation of Histamine From the Heart, Biochem. J. 24: 626, 1930.
48. Warburg, O.: The Metabolism of Tumors, London, 1930, Constable & Co.
49. Zeehuisen, H.: Sur la teneur en potassium, thorium, ionium, et urane des coeur battant dans des solutions saline, Arch. néerl. de physiol. 11: 386, 1926.
50. Zwaardemaker, H.: Physiological Radioactivity, J. Physiol. 53: 273, 1920; ibid. 55: 35, 1921; Replacement of Potassium by Uranium in Perfusion of Heart, Arch. néerl. de physiol. 4: 177, 1921; ibid. 5: 285, 1921.
51. Idem: Die Bestrahlungschelle bzw die innere Schwelle des Ursprungsreizes im Herzen, Pflüger's Arch. 217: 1, 1928; Ueber die Strahlungsstoffe im Herzen, ibid. 218: 354, 1928; Arch. néerl. de physiol. 12: 502, 1928; Der Elektrokardiogram des Automatinherzens, Pflüger's Arch. 221: 455, 1929.

Selected Abstracts

Wood, Francis Clark and Wolferth, Charles C.: Experimental Coronary Occlusion. Arch. Int. Med. 51: 771, 1933.

The dog presents a situation analogous to that existing in man, with respect to occlusion of the coronary arteries. Infarction in some parts of the heart produces a deviation of the RS-T interval from the isoelectric line in the conventional electrocardiogram. Infarction in other parts of the heart does not.

Electrograms show that the failure of certain infarcts to affect the limb lead electrocardiogram is not due to a failure of the development of changes in the action current in the infarcted area. By means of direct heart leads, deviations of the RS-T interval are recordable within a few minutes after infarction of any part of the surface of the heart.

If conduction from all surfaces of the heart is adequate and if an anteroposterior chest lead is used in addition to the routine limb leads, a deviation of the RS-T interval can be recorded in one or more leads after occlusion of any one of the three main coronary arterial trunks. This is likewise true of occlusion of some of the branches of these arteries.

Deviation of the RS-T interval due to occlusion of the left anterior descending coronary artery appears in only one of these four leads, the anteroposterior chest lead. Likewise, in man, infarcts in some parts of the heart fail to produce deviations of the RS-T interval except in certain leads which heretofore have not been used as a routine measure.

When the right and the left arm lead wires are used and when the electrodes are placed on opposite sides of the chest, an infarct located beneath the former produces a depression of the RS-T interval; one located beneath the latter produces an elevation of this interval. The direction of the deviation of the RS-T interval and the lead in which it makes its maximum appearance serve to indicate the location of the infarct. It is therefore probable that more accurate electrocardiographic localization of myocardial infarcts may be attained in man by the use of chest leads in addition to the three conventional ones.

Deviations of the RS-T interval after coronary occlusion in the dog appear within two minutes. It is not likely that they take much longer to appear in man.

No additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviation of the RS-T interval beyond that produced by occlusion of a coronary artery.

The size of an infarct necessary to cause changes in the RS-T interval, recordable from the body surface, has not been determined accurately. It is certain, however, that relatively small infarcts suffice. The optimum points of application of the electrodes for recording electrocardiographic changes after obstruction of the various coronary arteries deserve further investigation.

This series of experiments demonstrates that in the dog deviation of the RS-T interval from the isoelectric line is a characteristic result of acute infarction of any part of the surface of the heart. Failure to record this electrocardiographic change in previous similar experiments has often been due to failure to apply the electrodes to the surface of the body in the proper locations.

The necessity for augmenting the three conventional leads is apparent if a more nearly adequate electrocardiographic picture of cardiac events is to be obtained.

The authors also point out the relative immediate danger to the dog of clamping the various coronary arteries. Ventricular fibrillation is the usual terminal event in experiments on coronary occlusion. It occurs most rapidly when the left posterior circumflex artery is occluded, within three or four minutes as a rule. It develops more slowly after obstruction of the left anterior descending artery. The least danger of early fibrillation seems to result from right coronary occlusion. Clamping of both the right and the left anterior descending arteries did not seem to be as immediately dangerous to the life of the animal as clamping of the left posterior circumflex alone. The authors do not understand the reason why occlusion of the latter artery should be particularly prone to cause ventricular fibrillation. The question arises as to whether there is an area in the distribution of this artery which, when deprived of its blood supply, is especially likely to cause fibrillation of the ventricles. The coronary sinus and the inferior vena cava may be clamped for relatively long periods without endangering the life of the animal.

Barton, E. M., and Greenwood, H. H.: Experimental Infarction of the Interventricular Septum of the Canine Heart. Arch. Path. 16: 15, 1933.

When the front septal branch of the left coronary artery of the dog was occluded by ligation and when the animals had recovered from the immediate effects of the operation, a typical infarct was produced in the interventricular septum and usually in part of the auriculoventricular node as well. Some of the ganglion cells and ganglion cell groups in such infarcted nodes had undergone degenerative changes.

No permanent interruption of conduction as a result of these lesions was discoverable by electrocardiograms. Mural thrombosis of the cavities of the heart was not observed. Among the possible reasons for the paucity of the conduction disturbances are the richness and the variability in the arterial blood supply to the conduction system of the dog and the frequency with which the endocardium and the Purkinje fibers over the infarcts were found intact.

Dock, William: Mode of Production of the First Heart Sound. Arch. Int. Med. 51: 737, 1933.

Experiments on the exposed hearts of dogs demonstrate that there is no muscular element in the first heart sound and that ventricular systole produces no audible vibrations, in either empty or full hearts, if tensing of the auriculoventricular valves is prevented.

A comparison of the pressure changes in the auricles and the rate of outflow through the atrioventricular valves with the period at which first sounds are accentuated by a previous auricular systole shows the importance of the position of the auriculoventricular valves in determining the loudness of the first sound. If the valves are closed and intraventricular pressure about as high as that in the auricle, ventricular systole causes only a faint sound; if the valves are slack and displaced toward the ventricle by the rush of blood through them, ventricular systole produces a loud first sound.

The author, therefore, concludes that the first heart sound is due to suddenly putting under high tension the previously slack fibers of the auriculoventricular valves. If the valves are closed and the slackness is taken up gradually before

ventricular systole occurs, the intensity of the sound is greatly diminished. The factors determining loudness of the first sound are, therefore, the degree of tension in the valves when ventricular systole occurs and the rate of rise of intraventricular tension.

Greene, J. A., and Coggeshall, H. C.: Clinical Studies on Respiration. I. The Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man. Arch. Int. Med. 52: 44, 1933.

The plethysmographic method for the study of the respiratory movements in man has been described. The false results obtained by the method are discussed.

The expiratory position of the chest in repose is more constant than the inspiratory position, but the expiratory position may also fluctuate in apparently normal subjects. After the subject has become accustomed to the procedure, the volume of air in the lungs at the end of expiration increases immediately when the body is changed from the horizontal to the vertical position and decreases immediately when the body is returned to the horizontal position. The expiratory position of the chest may or may not increase with slight muscular work. If it increases, the time required for it to return to its previous level varies. The expiratory position of the chest and the depth of the respirations during talking and reading aloud appear to depend on the length of the sentences and phrases when the subject is at ease and when hyperventilation may occur.

Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration. II. Influence of Determination of Basal Metabolism on Respiratory Movements in Man, and Effect of These Alterations on Calculated Basal Metabolic Rate. Arch. Int. Med 52: 226, 1933.

The influence of the determination of the basal metabolic rate on the respiratory movements has been studied in three normal and twenty diseased subjects. The respiratory movements may be altered in rate, rhythm, amplitude, or expiratory position of the chest, or in several combinations of these. The respiratory movements were altered in every subject during the determination of the basal metabolic rate, and the ventilation was increased in twenty subjects, unchanged in one, and questionably altered in two. The manner in which the respiratory movements are altered varies with different subjects and may vary with the same subject during different examinations. Changes in the expiratory position of the chest may alter the basal metabolic rate as determined by the closed circuit method. The decreased excretion of carbon dioxide by some subjects in the basal state may be due in part to changes of the expiratory position of the chest.

Alterations of the expiratory position of the chest may explain some of the variances between the determinations of the basal metabolic rate and the clinical findings. The alterations in the determinations of the basal metabolic rate due to changes of the expiratory position of the chest would be materially decreased if longer test periods were used.

Hurtado, Alberto, and Boller, Charles: Studies of Total Pulmonary Capacity and Its Subdivisions. I. Normal, Absolute and Relative Values. J. Clin. Investigation 12: 793, 1933.

Determinations of total pulmonary capacity and its subdivisions have been made in fifty normal young males. Christie's method of oxygen dilution without

forced breathing was used, and his classification adopted. All determinations have been made with the subject in a recumbent position after a preliminary period of rest. The age and physical characteristics of the subjects are fully presented.

The results obtained suggest that there are wide variations in the absolute values of the total pulmonary capacity and its subdivisions. The vital capacity, residual air, and midcapacity fluctuate within well-defined limits if expressed as a percentage of the total volume. If the vital capacity is less than 65 per cent of the total volume, or if similarly the residual air is higher than 35 per cent, an impairment in the alveolar ventilation must be suspected.

The constant normal ratios found between the total pulmonary capacity and its main subdivisions suggest that alterations in these ratios may give a quantitative estimation of the degree of functional respiratory efficiency from the point of view of alveolar ventilation.

Hurtado, Alberto, and Fray, Walter W.: Studies of Total Pulmonary Capacity and Its Subdivisions. II. Correlation With Physical and Radiological Measurements. J. Clin. Investigation 12: 807, 1933.

In the present communication the correlations between the total capacity and its main subdivisions with height, weight, surface area, and external and radiological measurements of the thorax are discussed. It has been shown that they may be calculated best in a given case from the so-called radiological chest volume. The method of calculation is fully presented. Comparison of the observed and the calculated volumes shows a very close correspondence. The application of these observations allows one to recognize pathological deviations. Studies have been made of the normal variability in the degree of expansion of the chest which is best exhibited by measurements of the chest film taken by means of a standard, the technic of which has been described. The same film together with the measurement of the anteroposterior diameter of the chest at maximum inspiration furnished all necessary information for the calculation of a given pulmonary capacity if correlation, coefficients, and regression formulas are used. The influence of the shape of the chest has also been investigated. The observations lead to the following conclusions:

When the total pulmonary capacity and its main subdivisions are calculated on the basis of the radiological chest volume, at maximum inspiration, the following deviations in the observed values (as compared with the calculated ones) are considered to be significant: a difference of over 15 per cent in the total pulmonary capacity and vital capacity and of 30 per cent and 40 per cent in the midcapacity and residual air respectively.

If the ratio: (Area at maximum expiration/Area at maximum inspiration) $\times 100$ is higher than 72.0, a reduction in chest expansion is indicated. Further evidence of deficient expansion is obtained if the diaphragmatic excursion, the lateral expansion, and the degree of movement of the ribs are found to be less than 4 cm., 2 cm., and 12° respectively.

There is a certain correlation between the degree of chest expansion (as appreciated by the ratio mentioned) and the relative proportions of subdivisions of the pulmonary capacity. Deficient expansion tends to be accompanied by a higher percentage of the residual air in relation to the total capacity.

There is a relationship between the shape of the chest and the capacity of the lungs. Persons with broad, muscular chests and high diaphragms (hypersthenic type) usually present low volumes of reserve air, as compared with long and narrow-chested persons with low diaphragms (asthenic type). The latter have larger thoracic capacity and consequently larger pulmonary capacity.

From the observations made on normal males, it is possible to detect pathological changes in the absolute and relative pulmonary capacity in a given case. The importance of recognizing such alterations is obvious.

Hurtado, Alberto, and Fray, Walter W.: Studies of Total Pulmonary Capacity and Its Subdivisions. III. Changes With Body Posture. *J. Clin. Investigation* 12: 825, 1933.

The effects of posture upon the pulmonary capacity and the size and expansion of the chest have been observed in ten healthy males by comparing measurements made in recumbent and sitting postures. It has been found that when recumbent there are slight decreases in the total volume, the vital capacity, and the residual air, but the reserve air decreases markedly. On the other hand, there is a marked increase in the volume of the complementary air. Similar and parallel decreases, although proportionally less marked, have been demonstrated to occur in the size of the chest. This diminution is most marked at midcapacity, and it is caused by an upward displacement of the diaphragm. An analysis of the expansion of the chest in both sitting and recumbent positions shows also parallel changes. In the latter posture the diaphragmatic excursion and the change in the area of the projection of the lungs corresponding to the reserve air are considerably reduced, while the reverse is true in relation to the complementary air.

These observations furnish additional data regarding the close correlation existing between the pulmonary capacity and the size and expansion of the chest and indicate the necessity for adopting a standard posture when investigations of this nature are made.

Hurtado, Alberto, Fray, Walter W., and McCann, William S.: Studies of Total Pulmonary Capacity and Its Subdivisions. IV. Preliminary Observations on Cases of Pulmonary Emphysema and of Pneumoconiosis. *J. Clin. Investigation* 12: 833, 1933.

In seven of nine cases of pulmonary emphysema, the total pulmonary capacity observed corresponded closely with that predicted from measurements of the chest cavity. In two it was slightly less. Increase in the volume of the residual air and a corresponding reduction in the vital capacity was observed in all the cases. In emphysematous patients there was a definite reduction in expansion of the chest, the degree being closely correlated with alterations in the relative pulmonary capacities.

In cases of pneumoconiosis, the total capacity of the lungs observed was less than that predicted from measurements of the chest due to decrease in the vital capacity. The residual air was moderately increased in four of five cases. In one the changes were minimal. Decrease in expansion of the chest was not a significant feature of cases of pneumoconiosis. Cases in which the ratio was abnormally high were found to exhibit low saturation of the arterial blood with oxygen, indicating poor alveolar ventilation.

Preliminary observations on response to exercise showed that the capacity to ventilate the lungs was limited in a severe case of emphysema and in one of pneumoconiosis compared with that in a normal man. Further observations will be necessary to establish a relationship between the degree of functional disability and abnormalities in pulmonary capacity.

Coburn, Alvin F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues. *Am. J. Dis. Child.* 45: 933, 1933.

The present study has been made on a group of 320 patients who died with rheumatic disease and who were examined post mortem. Particular interest is in a group in which death occurred during activity of the rheumatic process, showing alterations in the tissues as a result of the rheumatic infection. Hemorrhagic lesions without distinctive histologic structure were conspicuous. The character of these nonspecific lesions suggested the activity of a single process with varying degrees of intensity: (1) engorgement of the blood vessels; (2) alteration in the permeability of the vascular tissues with diapedesis, but without a demonstrable change in the structure; (3) an inflammatory reaction. The damage to the tissue in the patients with acute rheumatism was characterized by the absence of detectable microorganisms and commonly by vasodilatation, swelling of the endothelium, necrosis of the collagen, infiltration with various wandering cells, and especially hemorrhage. During the first cycle of the rheumatic attack, few or no Aschoff bodies were detected in the cardiac muscle; however, the presence of specific lesions in the endocardium established the diagnosis.

When the rheumatic subject is infected with the hemolytic streptococcus, the initial response is of the usual clinical character. If the infection is limited to the upper respiratory tract, recovery occurs within a few days. This illness, though mild, may nevertheless be the first phase in the development of a severe rheumatic attack.

Following the subsidence of the local infection, the patient usually regains his customary health, and nothing abnormal is detected clinically. This quiescent interval of days or a few weeks represents the second phase in the evolution of the rheumatic process. The second phase persists until a rise in the titer of immune bodies is detected in the blood of the peripheral circulation. Almost simultaneously with this response of the immunity mechanism, the rheumatic process is activated in susceptible persons.

When the rheumatic process is activated, the initial response is characterized by manifestations of a hemorrhagic nature. Particularly common at this stage are epistaxis and the erythemas; while melena, hemoptysis, and hematemesis also occur. Studies of the excretion of erythrocytes in the urine indicate the close relationship of hemorrhage to the activity of the rheumatic process. Late in the attack, when symptoms are subsiding and the abnormal urinary observations have disappeared, there may be a second stage, characterized clinically perhaps only by the appearance of subcutaneous nodules.

The author believes, therefore, that the evolution of rheumatic fever consists of, first, a phase in which there is an infection of the respiratory tract with a hemolytic streptococcus, and second, a symptom-free phase in which the immune response develops in the rheumatic subject, and finally, the acute attack. During the third phase, activity of the rheumatic process is characterized clinically by a tendency to hemorrhage which was well correlated with the anatomic observations in the cases studied.

Grollman, Arthur, Friedman, Ben, Clark, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients With Cardiac Disease. *J. Clin. Investigation* 12: 751, 1933.

A critical study has been made of the possible sources of error of the Burwell-Robinson, venous plateau, and acetylene methods for measuring the cardiac out-

put which may invalidate the results obtained when applying them to patients with congestive heart failure. The methods to be used for detecting and avoiding these errors are indicated. Results as obtained by these different methods are given.

As to the relative merits of the method studied, the laboriousness of the Burwell-Robinson and venous plateau methods both to the patient and to the investigator renders them inferior to the relatively simple acetylene procedure. In persons with normal arterial oxygen saturation, the practice of taking three samples as advocated for the acetylene method should exclude the possibility of error. With care, moreover, the method will be found to be applicable to a large percentage of subjects with advanced cardiac disease and with mild congestive failure. In those subjects in whom the method is not applicable, the venous plateau method may be applied. Unfortunately, it is in these very cases that the pitfalls inherent in the latter method occur and great care and labor are required to avoid them.

Wolff, Louis: Angina Pectoris (or Status Anginosus) and Cardiac Asthma Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia. *New England J. Med.* 208: 1194, 1933.

The author describes four patients in whom angina pectoris (or status anginosus) and cardiac asthma were induced by paroxysmal auricular fibrillation and paroxysmal tachycardia. This condition should be differentiated from angina of effort in coronary thrombosis, and the difficulties encountered in such differentiation are discussed. Embolism, fever and leucocytosis may sometimes occur with or follow paroxysmal arrhythmias and consideration which must be reckoned with in the study of patients with pain suggestive of coronary thrombosis.

The cardiovascular changes which occur during a paroxysmal arrhythmia favor vascular thrombosis, and it must be recognized that in the face of coronary artery disease, coronary thrombosis may be induced by paroxysm of rapid heart action. The prevention or curtailment of such paroxysms by quinidine and other methods offers a prophylactic measure against coronary thrombosis in a small number of patients.

Sproull, John: The Simulation of Coronary Thrombosis by Angina Pectoris Induced by Paroxysmal Tachycardia. *New England J. Med.* 208: 1198, 1933.

Two cases of angina pectoris induced by paroxysmal tachycardia and closely resembling cases of coronary thrombosis are reported. Because of the difficulties of establishing a diagnosis of paroxysmal tachycardia as a cause of angina pectoris, it appears that the proper and safe procedure is to treat suspected cases as if coronary thrombosis were present, reserving the ultimate diagnosis until all possible evidence has been accumulated and considered. On account of the similarity of the two conditions and also for the reason of the variation in their prognosis and care, a complacent acceptance of the diagnosis of coronary thrombosis in attacks of severe angina pectoris with tachycardia is to be avoided. As in other instances, the failure to have the condition in mind causes some errors in diagnosis.

Ayman, David: The Personality Type of Patients With Arteriolar Essential Hypertension. *Am. J. M. Sc.* 186: 213, 1933.

A study has been made of the personality of 182 patients consisting of middle-aged hypertensive patients, hypertensive patients between the ages of eighteen

and thirty-five, middle-aged normal subjects with normal blood pressure, and young normal subjects with normal blood pressure. The results indicate that hypertensive subjects tend to have a distinct type of personality. Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals with a large and steady output of energy. They tend to be sensitive and quick-tempered. The mood fluctuations, however, are not an important feature, which differentiates them from the manic-depressive individuals. The hypertensive personality has existed as far back as the subject can remember.

Lundy, Clayton J., and Bacon, Charles M.: Premature Left Ventricular Beats From Electrical Stimulation of Exposed Human Heart. Arch. Int. Med. 52: 30, 1933.

The authors had the opportunity of studying a four-year-old child in whom a purulent pericardial effusion developed following influenza of the upper respiratory tract, and pericardiotomy had been performed through the left half of the sternum, at the level of the fourth and fifth rib. Through the operative wound could be seen the left auricular appendix and the basal portion of the left side of the ventricles.

Electrically induced extrasystoles from the base and apex of the left ventricle gave discordant QRS complexes. The extrasystoles arising from the base were upright in Lead I and inverted in Lead III. Those arising from the apex were inverted in Lead I and upright in Lead III. The ventricular extrasystoles elicited from a point designated as I is from a region heretofore unexplored.

Ayman, David, and Krakower, A.: Influence of Sclerotic Arterial Wall on Blood Pressure Measurements. Arch. Int. Med. 52: 33, 1933.

Simultaneous bilateral readings of the blood pressure in the radial arteries were made in a patient who both clinically and radiographically had a soft radial vessel on one side and a sclerotic radial vessel on the other side. The results are in accord with evidence obtained previously in studies with excised vessels, and the observations indicate that the sclerotic arterial wall has no significant effect on the determination of blood pressure. It was also found that in this patient, as well as in three other patients with marked radial sclerosis, the radial blood pressure reading was higher than the brachial blood pressure reading.

Solomon, Philip, Hurwitz, David, Woodall, Martin, and Lamb, Marion E.: Diagnosis of Gonococcus Endocarditis. Arch. Int. Med. 52: 1, 1933.

A case of gonococcus endocarditis is reported in detail. The diagnosis of acute vegetative endocarditis was made clinically and was proved at autopsy. The organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin, and complement fixation reaction.

The condition occurred in a patient during the last days of pregnancy with symptoms of an upper respiratory tract infection. Following a bronchopneumonia, the temperature continued high and the pulse rate rose to 140. Two days later chills and hemiplegia and signs of endocarditis developed. The spinal fluid was blood tinged and had 4,000 white blood cells per cubic millimeter. The organisms

were not recovered from the meningeal fluid. It is pointed out that gonococcus septicemia occurs fairly frequently and often is followed by recovery, but when endocarditis develops, the issue is grave.

Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease. Arch. Int. Med. 52: 16, 1933.

Two factors, the duration and the type of myocardial failure, are mainly responsible for the occurrence of pulmonary infarction. The lowest incidence of infarction occurred in patients with subacute bacterial endocarditis in whom congestive heart failure rarely occurs, and in those with primary failure of the right side of the heart, in whom the left side is usually competent until the end. The highest incidence occurred in the group with rheumatic cardiovascular disease, mostly in those with disease of the mitral valves. This group also showed a longer duration of heart failure. Long-standing pulmonary congestion, therefore, is a significant factor in the causation of pulmonary infarction.

The data indicate that jaundice is not directly correlated with the degree of anoxemia induced by pulmonary infarction. If it were true that the occurrence of frank jaundice depended wholly on the existence of an advanced degree of anoxemia, a much higher incidence of jaundice would occur in the cases of multiple and massive infarctions and of lobar pneumonia. Yet the existence of a pulmonary infarct appears to be an almost indispensable factor in the causation of clinical jaundice, occurring in 94 per cent of the cases. However, a combination of circumstances and factors is necessary.

In addition to long-standing pulmonary congestion, a higher incidence of anatomic lesions of the liver and of systemic or pulmonary infection is found in the patients with jaundice. A survey of the anatomic lesions of the liver and studies of the function of the liver make it apparent, however, that unless true cardiac cirrhosis or diffuse inflammatory vascular disease of the liver exists, the jaundice is not primarily of hepatic origin. Infection either systemic or pulmonary also plays an important contributory rôle, probably by influencing the rate of formation and resorption of bilirubin from its source, the pulmonary infarct, and the rate of its excretion by the liver.

Stroud, William D., Goldsmith, Melville A., Polk, D. Stewart, and Thorp, Francis Q.: Ten Years' Observation of Children With Rheumatic Heart Disease. J. A. M. A. 101: 502, 1933.

The present study of the condition of 458 children cared for at the Children's Heart Hospital in Philadelphia during a ten-year period from June, 1922 to January, 1932, with a more intensive study of some 141 children in this group selected because of the more complete data available in their case histories, may help to answer the query and at the same time, offer a contribution of additional information concerning rheumatic fever in children.

The average age of the primary manifestation of rheumatic fever in this group has been 7.3 years. Of the 307 children concerning whom information was available, 125 are dead or totally disabled and 182 are working or able to work or go to school. Of a total of 428 primary manifestations and reactivations concerning which positive information is available, 61 per cent occurred during and between the months of December and May with a peak of 15.2 per cent during March. It is suggested that during these months, prophylactic measures should be especially stressed in susceptible children between the ages of six and ten years, the years during which primary manifestations and reactivations are most

apt to occur. In this group, by far the greatest number of patients were of Italian, Hebrew, American, and Irish parentage, in the order named. There seems to be a familial incidence at least as high as that in tuberculosis.

Accurate information as to the incidence of common colds, sore throats, and other infections of the respiratory tract in other members of the family and their relationship to primary manifestations and reactivations of rheumatic fever cannot be obtained by questioning the child or his parents unless this problem and its possible importance has been carefully explained beforehand and frequently reiterated to the patient and each member of the family. Measures to protect children with rheumatic heart disease from the common cold and other infections of the respiratory tract offer as far as the study has shown, the most practical form of prophylactic treatment that at the present time can be freely recommended. The use of intravenous preparations of hemolytic streptococci with the hope of lessening hypersensitivity is still in the experimental stage but offers much promise.

Although positive proof that the routine removal of tonsils prevents primary manifestations or minimizes reactivations of rheumatic fever is not clear, it is felt by the authors that such a procedure plus a careful study of the sinuses is still justified in the type of child included in this study.

Premature contractions were found with relative infrequency in this group and auricular fibrillation was usually a terminal or near terminal event. The valve or number of valves involved in rheumatic heart disease in childhood has little to do with prognosis as compared to the virulence of the infection, the resistance of the host, and the number of reactivations.

It is felt, in conclusion, that a continuance of the treatment of children with rheumatic heart disease in convalescent hospitals in those areas in which rheumatic fever is prevalent is still justified.

Kugel, M. A., and Stoloff, E. Gordon: Dilatation and Hypertrophy of the Heart in Infants and in Young Children. *Am. J. Dis. Child.* 45: 828, 1933.

A complete review of the literature of congenital idiopathic hypertrophy of the heart has been made and the 52 cases found have been analyzed. In addition, the complete clinical, roentgenological, and pathological study of 7 additional cases from the authors are described. A careful study revealed that of these 52 cases only 17 were apparently associated with pure hypertrophy of the heart muscle both on gross and microscopic examination. In the light of the authors' experience with the 7 additional cases of dilatation and hypertrophy of the hearts in infants and children, all the cases reported in the literature have been re-examined.

In the cases studied, careful histological examination of the heart muscle showed uniformly similar pathological changes in the group of cases generally called congenital idiopathic hypertrophy of the heart. These pathological changes are degeneration and atrophy of cardiac musculature, replacement, fibrosis, scarring of the myocardium, endocardial fibrosis, and vascular changes. A thorough analysis of the roentgenograms was made in 4 cases. Significant electrocardiographic changes have been reported in one case. It seems from this study that the group of cases of so-called congenital idiopathic hypertrophy is probably seldom, if ever, idiopathic as has been demonstrated with the newer knowledge of the pathology and of the other factors causing dilatation and hypertrophy of the heart.

When the hearts are examined by the standardized sections of Gross, Antopol and Sacks and also numerous sections along the coronary arteries, it is possible to find myocardial degeneration and fibrosis.

Blumgart, Herman L., Riseman, Joseph E. F., David, David, and Berlin, David D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity. *Arch. Int. Med.* 52: 165, 1933.

This communication is a report on the therapeutic results of total ablation of the normal thyroid gland in a series of ten patients with congestive heart failure or angina pectoris. The clinical observations which provided the rationale for this procedure are as follows: Measurement of the velocity of blood flow through the lungs in more than 600 subjects demonstrated that normally the velocity of flow was directly determined by the metabolic demands of the body. The metabolic demands of the body were gauged by the basal metabolic rate. When the metabolic rate was accelerated, as in thyrotoxicosis, the speed of blood flow was proportionately increased; on the other hand, when the metabolic rate was depressed, as in myxedema, the blood velocity was correspondingly lowered. Patients with compensated heart disease were found to have a blood velocity within normal limits, in accord with the normal level of the basal metabolic rate. But in subjects with congestive heart failure, in spite of a normal metabolic rate, the blood velocity was considerably slowed. This lack of correspondence offered an explanation for the presence of the symptoms and signs of decompensation which were in proportion to the degree of slowing of the blood velocity. The corollary of these observations was obvious: since therapeutic attack directed toward the circulation in chronic heart failure is unavailing, the way to relieve the circulation is to decrease the load on it by lowering the basal metabolic rate, i.e., by thyroidectomy. Subtotal thyroidectomy produced only temporary improvement.

Attacks of angina pectoris, which were present in two patients before operation, have not recurred since complete thyroidectomy. In one of these patients, before operation the same measured amount of work under standard conditions regularly precipitated attacks. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion. Seven of the nine patients with congestive heart failure had practically no cardiac reserve after prolonged periods of adequate medical treatment with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation.

During the period of observation of three to six months that have elapsed since operation, all of the patients have shown conspicuous improvement. They have been able to undertake from slight to considerable exertion without the development of palpitation, dyspnea or any signs of congestive failure. The preoperative craving for water has disappeared. The basal metabolic rate of each patient has shown a significant and persistent lowering which has paralleled the most striking improvement. The velocity of blood flow has become slower in seven patients, indicating that the heart is required to do less work under the new postoperative condition than it was able to accomplish when the metabolic rate was normal. These patients may therefore be regarded as being in possession of a definite "cardiac reserve." The vital capacity of the lungs showed a decided increase in some patients though not in all. The significance of these findings is discussed. By means of exercise tests standardized for each of the nine persons with congestive failure, an increased ability to perform light work after operation has been demonstrated. Frequently recurring hemoptysis and pain in the chest have disappeared following operation. One patient who suffered

from paroxysmal dyspnea showed improvement for three weeks following operation. On the twenty-second day, he suffered from an attack of acute pulmonary edema during which he died. Further experience is necessary to evaluate the possible benefit to be derived from thyroidectomy in this condition and operation should be undertaken in this type of cardiovascular disease with extreme caution.

Following operation patients have had slight dryness of the skin, increased sensitivity to cold, slow growth of hair, and a lower heart rate. Thyroid substance has not been given except for short periods to two patients; in the others, it has not been indicated thus far. The medical management of the operative course is described. In one patient with congestive failure who had suffered from continuous attacks of bronchial asthma since childhood, no severe attacks have occurred since operation. The possible beneficial effects of the procedure in other conditions are discussed.

Because of the inevitable uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris, in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, vascular accidents, repeated pulmonary infarctions or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

Ryland, David A.: The Effect of Digitalis on the Venous Pressure of Normal Individuals. J. Clin. Investigation 12: 847, 1933.

Digitalis causes in normal human beings and dogs a decreased cardiac output and a decreased venous pressure. The greatest effect occurs at about twenty-four to thirty-two hours after administration of the drug with a return to normal level in from seventy-two to ninety-six hours.

The observed changes support the hypothesis that digitalis owes its action to a peripheral effect, probably on the hepatic vein radicles in reducing the return flow of blood to the heart. The hypothesis that the digitalis action follows changes in the cardiac tone is not supported by all available data. Digitalis bradycardia is not due to the fall of venous pressure; on the contrary, the slowing of the heart by causing the normal increase in venous pressure, partially conceals the effect of digitalis in reducing the return flow of blood to the heart.

Lehman, A. J., and Hanzlik P. J.: Comparative Potency of Some Digitalis Specialties According to the Pigeon Method. J. Pharmacol. and Exper. Therap. 48: 151, 1933.

The potency as indicated by the minimum emetic and fatal doses for pigeons of several digitalis specialties has been compared with official tinctures from an American leaf and from an international powder used as standards. All the specialties caused emesis, their potency varied considerably, their keeping qualities during periods of months were good in the majority of cases but three of the specialties weakened considerably, their fatal doses varied considerably, and, in general, the killing power of the weaker specialties was out of proportion to their emetic efficiency, confirming previous results with ordinary digitalis. These specialties are no freer from side actions and have no special advantages over the ordinary official powder or tincture for general therapeutic uses except possibly the injection feature which may be useful in occasional special cases where

oral administration is impossible or undesirable and when emergency medication is indicated. The fact that some of the specialties do not keep nearly as well as the ordinary tincture is decidedly against them.

Tolerance to the emetic action of digitalis is demonstrable in pigeons which have been reinjected six times consecutively for ten weeks in agreement with reported loss of emetic action in reinjected dogs and cats. The tolerance does not impair the usefulness of pigeons for biological essay.

Schmitz, Henry Lenzen: Studies on the Action of Diuretics. II. The Effect of Salyrgan Upon the Water Content of the Plasma as Measured by the Refractive Index. J. Clin. Investigation 12: 741, 1933.

The effect of salyrgan upon the water content of the plasma has been studied by means of the refractometer in dogs. There is no evidence in the experiments that salyrgan diuresis is preceded by a mobilization of fluid from the tissue spaces. The results point strongly to a primary direct action of salyrgan on the kidney with a secondary inflow of fluid from the tissue spaces to prevent excessive dehydration of the plasma.

Weiss, Soma, and Ellis, Laurence B.: Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity. Arch. Int. Med. 52: 105, 1933.

The study concerns the effect of large therapeutic doses (from 1 to 5 grains) of sodium nitrite by mouth on ten normal persons, twenty-nine patients with primary arterial hypertension, five patients with glomerulonephritis, and nine patients on whom unilateral nephrectomy had previously been performed. Qualitatively the effect was the same in each group, but there were certain quantitative differences between the normal subjects and those with hypertension and renal disease.

The nitrite inconstantly produced symptoms, an increase in cardiac rate and a depression of blood pressure and renal function. No simple correlation was found between these factors except when they were markedly altered.

A decrease of systolic blood pressure was the most frequently observed effect of sodium nitrite. This was caused probably by dilatation of certain parts of the arterial system. The greater the initial degree of arterial tonus, the greater was the drop in systolic pressure. With arterial hypertension, this was particularly evident.

In five normal persons sodium nitrite produced no change in the minute volume output of the heart. In five patients with arterial hypertension this output was doubtfully reduced in three, and reduced 15 and 32 per cent respectively in two. In nine of these ten subjects there was a reduction of the cardiac stroke volume output, which reached 15 per cent or more in six.

Sodium nitrite did not affect the basal metabolic rate of nine of ten subjects; it possibly increased the rate in one.

The effect of the nitrite on renal function was investigated thirty-five times by simultaneous determinations of the urinary output and urea and creatinine clearance tests. In no case was the renal capacity improved. In fourteen instances there was no change in renal function; thirteen times it was definitely decreased, and on eight occasions it was questionably lowered.

Physiologic changes which occur in the human cardiovascular system as a result of the action of sodium nitrite are discussed and correlated.

The use of sodium nitrite in the routine treatment of arterial hypertension with the hope of maintaining the blood pressure at a relatively low level is illogical and may be dangerous.

Evans, William, and Hoyle, Clifford: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris. *Quart. J. Med.* 2: 311, 1933.

A series of 90 patients with angina pectoris of effort was observed over a period of two and a half years, with special reference to the comparative value of certain drugs and medicinal remedies with any claim to be applied in continuous treatment. Syphilitic angina pectoris was excluded and coronary thrombosis was only considered as a complication.

Each patient attended fortnightly and the various drugs were administered over periods of two to four weeks at a time, or longer. In this way their effects upon the frequency and severity of attacks could be compared. As a control in each case a placebo was regularly substituted for an active drug. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, euphyllin, belladonna, digitalis, lacarnol, and harmol.

The comparative results are outlined in tables and graphs. With one exception, they show that a measure of improvement appears to result from every remedy tried and at least as great an improvement during treatment with placebo. This universal efficacy can only be explained by natural variations in the severity of the symptoms which give a spurious value to each remedy. If any drug had proved to be superior, there might have been grounds for recommending it in the continuous treatment of the disease, but no such precedence could be made out. Though scarcely convincing, there was some reason to think that chloral, morphine, papaverine and phenacetin had a trifling influence in controlling the group incidence and severity of attacks.

The authors were unable to find convincing evidence that any drug tested is worthy even of trial in the routine treatment of the disease. Though not widely applicable, a drug might of course be effective in individual cases, and examples were sought for, but, with a few exceptions, were not found. The nature of the underlying cause of angina pectoris alone would seem to make the quest for a satisfactory form of treatment on these lines unlikely of attainment.

If none of these remedies are capable of lessening the frequency or severity of anginal attacks, there is all the greater need for a study of the application of those general measures known to control them and to promote the wider use of vasodilators, such as trinitrin, which are so often successful in the palliative treatment or even in the prevention of particular attacks.

Starr, Isaac, Elsom, K. A., and Reisinger, J. A.: Acetyl- β -Methylcholin. *Am. J. Med. Sc.* 186: 313, 1933.

In experiments on 47 normal persons, acetyl- β -methylcholin chloride has proved to be a drug which when injected subcutaneously in suitable dosage exerts a prompt and vigorous action. A fall in blood pressure, a rise of pulse rate, flushing, sweating, and salivation are the outstanding effects. Given by mouth this drug has a milder effect than that following subcutaneous injections. Given by the former method, even in very large doses, it does not cause discomfort, although blood pressure and pulse rate changes have been noted. The dosage required to produce effects by mouth is so much larger than when given subcutaneously that the destruction of large amounts of the drug in the gastrointestinal system seems probable.

In animal experiments an intravenous injection of acetyl- β -methylcholin chloride has effects on the cardiovascular system essentially similar to those which follow acetyl cholin, but judging by the effects which follow subcutaneous injections into normal men, acetyl- β -methylcholin chloride is over ten times as

powerful. It can also be given by mouth, whereas acetyl cholin is ineffective when thus administered. It also lacks certain of the undesirable side effects of acetyl cholin. It is believed, therefore, that acetyl- β -methyleholin chloride should supplant acetyl cholin in all conditions in which that drug is used for therapeutic purposes.

Abbott, W. Osler: Acetyl- β -Methyleholin. II. The Action on the Gastrointestinal Tract in Normal Persons, in Abdominal Distention and in Certain Other Conditions. Am. J. Med. Sc. 186: 323, 1933.

Acetyl- β -methyleholin by whatever route given affects the gastrointestinal tract as well as the other viscera supplied by the parasympathetic system. This effect is most satisfactorily achieved by oral administration, secretory and cardiovascular activity dominating the picture after subcutaneous injection.

The usual gastrointestinal effects are an increase in tone and movement. This is not the case in the fasting stomach or in the small intestine during the period of falling pressure after subcutaneous injection. Beneficial clinical effects have been manifested by slight stimulation of gastric secretion in some cases of hypochlorhydria, by a comfortable laxative effect in most persons taking large doses by mouth, but chiefly by the relief of abdominal distention in certain instances in which the usual procedures have failed.

Starr, Isaac: Acetyl- β -Methyleholin. III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, With a Discussion of Its Action in Other Conditions. Am. J. Med. Sc. 186: 330, 1933.

Acetyl- β -methyleholin has been employed in the treatment of certain types of cardiovascular disease. This drug causes effects similar to those following stimulation of the vagus and other parasympathetic nerves. It also causes peripheral vasodilatation. After subcutaneous injection, it has a prompt and vigorous action. Given by mouth the effects are much milder. The untoward effects of the drug are described; they can be immediately abolished by atropine.

Injected subcutaneously the drug has caused the immediate termination of twenty-four attacks of paroxysmal tachycardia in 9 patients. In most of the attacks carotid pressure and other means had been tried unsuccessfully before the drug was given. In a few instances a combination of the drug's action and carotid pressure terminated attacks which could not be stopped by carotid pressure alone. Failure was very infrequent except when the dosage was inadequate.

The vascular spasm of Raynaud's disease when excited by mild degrees of cold was relieved or prevented by the action of the drug administered by mouth. The spasm following exposure to severe cold was but little affected. The discomfort of three such patients was in part ameliorated by taking the drug by mouth during cold weather.

The drug repeatedly caused a rise of the skin temperature of the feet in a patient with thromboangiitis obliterans. It caused a temporary reduction of blood pressure in most cases of hypertension. In one patient Cheyne-Stokes respiration was abolished by the drug. The possible utility of acetyl- β -methyleholin in certain other disease conditions is discussed.

Book Review

THERAPEUTIQUE MÉDICALE. VI. COEUR ET SANG. By MM. A. Lemaire, E. Donzelot, Ch. Aubertin, A. Clerck, G. Marchal, R. Boigey, M. Mouquin, P. Émile-Weil, A. Tzanck. Pp. 312. Masson & Cie. Paris, 1933.

This volume is the sixth in a series of seven which comprise a system of therapeutics prepared under the editorship of Professor M. Loeper. It is evident from the list of contributors that this volume represents the best modern French opinions concerning the therapy of diseases of the heart and of the blood. The volume is divided into four parts, the first of which comprises the drug therapy of the various types of cardiac disease and of syncope and is chiefly from the pen of Professor Loeper. The second part is a presentation of the dietetic régime for the treatment of the cardiopathies. The third deals with the treatment of arrhythmia and the fourth with diseases of the blood.

The material is well arranged and the discussion of the employment of the various therapeutic agents is preceded by a brief but clear résumé of the pathological physiology, of the symptoms and manifestations of the diseases, as well as by discussion of the chief points in the pharmacology of the agents recommended. The agents are divided into those of major importance, such as digitalis, ouabain, etc., those of minor importance, and those which, while not acting upon the heart or blood vessels in any specific manner, can be regarded as adjuvants.

The chapter on the treatment of the various forms of cardiac failure emphasizes almost exclusively the French viewpoint which gives special preference to the use of Nativelle's digitaline (the crystalline digitoxin of the Germans) and Arnaud's ouabain (crystalline strophanthin G.). Detailed directions are given for their dosage and administration which do not differ essentially from those employed by others. Much emphasis is laid upon the value of glucose and of calcium as supportive measures in the treatment of heart disease and measures which materially enhance the activity of the digitalis bodies. It is rather striking to note the seeming impunity with which the administration of insulin is advocated in the treatment of cardiac failure. This is based primarily upon the conception of the value of glucose as a nutrient to the heart, and the corollary, that its utilization is enhanced by the simultaneous administration of insulin. Throughout the book many remedies are advocated as adjuvants which have largely been rejected in America.

The section on diseases of the blood is rather too brief and is somewhat incomplete. The authors have entirely omitted the discussion of polycythemia vera, even though it was originally described by one of their own countrymen, Vaquez. The treatment of pernicious anemia is taken almost bodily from the work done in America.

While the book is well printed and well arranged, it is distinctly marred by the absence of any adequate bibliography and by the absence of an alphabetical index. The relatively small number of references which are given show a considerable number of seemingly careless inaccuracies. Despite these shortcomings, the volume is an excellent one and should prove of real value to those interested in the methods of treatment found best by the leading therapists of France.

C. E.

The American Heart Journal

VOL. IX

DECEMBER, 1933

No. 2

Original Communications

THE NATURE OF THE VASCULAR COMMUNICATIONS BETWEEN THE CORONARY ARTERIES AND THE CHAMBERS OF THE HEART*†‡

JOSEPH T. WEARN, M.D., STACY R. METTIER, M.D.,
THEODORE G. KLUMPP, M.D., AND LOUISE J. ZSCHIESCHE, A.B.
CLEVELAND, OHIO

THE existence of direct vascular communications between the coronary arteries and the chambers of the heart has been claimed and denied. Such evidence as has been presented in favor of the existence of these channels has been indirect and based largely upon experiments in which perfusions and injections of the coronary vessels were employed. The use of the same general methods variously modified has led others to deny the existence of channels between the coronary arteries and the heart chambers. If such channels do exist they almost certainly play a rôle in the circulation of the heart, but at the present time there is no agreement as to the nature or the importance of that rôle. It seemed wise, therefore, to study the vessels by injections and by the rather tedious method of serial sections and wax-plate reconstructions in order to establish their anatomical and histological structure. Such knowledge, if established, should be of definite value to those investigators who, in studying the physiology of the coronary circulation, have been compelled to make one of two assumptions; namely, that vascular channels between the coronary arteries and the atria and ventricles either do or do not exist.

*From the H. K. Cushing Laboratory of Experimental Medicine in the Department of Medicine of Western Reserve University School of Medicine and Lakeside Hospital, Cleveland, Ohio, and from the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

†The results reported in the first part of this paper (celloidin injection experiments) were carried out in 1928 while Dr. Mettier was working with me in the Thorndike Laboratory. The investigation has since been extended and completed in the H. K. Cushing Laboratory where Dr. Klumpp joined in the work. Miss Zschiesche assisted in the investigation throughout. J. T. W.

‡The expenses of this investigation have been defrayed in part by a grant from the E. F. Bourne Memorial Fund of the Department of Medicine, Western Reserve University.

It is proposed to present here histological and other evidence of the existence of direct vascular channels between the coronary arteries and the chambers of the heart, as well as the results of certain observations upon the histological nature of these communicating vessels.

The belief that the coronary arteries have direct vascular communications with the chambers of the heart is not a new one. The idea was first advanced by Raymond Vieussens in 1705 in a letter to Monsieur Boudin, Conseiller d'Etat, Premier Medicin de Monseigneur le Dauphin. Boudin's reply in which he acknowledged receipt of Vieussens' letter was dated July 9, 1705. Vieussens' letter was published in 1706.¹ In it he related how, in examining the depth of the roots of a large polyp which had formed in the right ventricle of the heart of a man who had died of a slow fever accompanied by violent palpitation of the heart, he traced the firmest roots of the clot as far as certain holes which seemed to him to be the orifices of specific ducts. He made several similar observations and from them concluded that blood circulating in the medial and inner fleshy vessels of the heart was carried into the cavities by the ducts in which the polyps first take root. Next he injected saffron dye, dissolved in spirits, into the left coronary artery and observed its passage into the left atrium and left ventricle, but none escaped via the veins into the right chambers. He called these communicating vessels "fleshy" ("le reste est poussé en partie dans le ventricule gauche de ce viscere par des vaisseaux, que j'appellerai charnus cy-après"). Vieussens also dissected human hearts and the hearts of sheep and calves, and, with the aid of a microscope, found the small openings (ouvertures) in the chambers of all, in some instances with delicate valves over the openings while in others valves were lacking. He noted that many of the channels (conduits) received blood from several fleshy vessels. To these he gave the name "common vessels" and to their orifices the name "common openings" ("je les appelleray des vaisseaux communs: j'appelleray aussi leurs embouchures des ouvertures communes").

These vessels and openings, so clearly described by Vieussens, have since been confused with somewhat similar ones described by Thebesius² two years later in 1708, and as a result all such vessels are now commonly known as thebesian veins. Thebesius injected certain substances into the coronary veins and noted their escape into the heart cavities through small openings in the endocardium. He was familiar with Vieussens' work and so states in his paper.

Thebesius' belief that the vessels were connected only with veins was supported by several anatomists of the day and Vieussens' work was soon forgotten. Lancisi³ in 1740 injected mercury into the coronary arteries and observed its appearance in the heart chambers, but believed with Thebesius that it escaped through venous channels (thebesian veins). In 1798 John Abernethy,⁴ by making a "common coarse waxen

injection" into the coronary arteries, observed that it flowed readily into the cavities of the heart. He also injected masses of a different color into the arteries and veins and concluded that vessels from arteries and veins communicated with the heart chambers "because the injection which was employed was too coarse to pass from one set of vessels to the other, and yet the different colored injections passed into the cavities of the heart unmixed."

Then followed a period that might be termed the dark ages for the "vaisseaux charnus" and the thebesian veins, but it came to an end with the work of F. H. Pratt⁵ in 1898 who, by means of perfusion of defibrinated blood through the ventricle of a cat's heart, kept it beating for an hour. This very important work furnished the first experimental evidence that the thebesian vessels might serve as an entrance for blood from the ventricles into the capillaries.

In 1928, Wearn⁶ perfused the coronary arteries of human hearts with India ink and observed that the perfusate for the most part escaped into the chambers of the heart through the thebesian vessels. Histological sections of these hearts revealed the fact that very few, and in many instances scarcely any, of the capillaries contained ink particles. Moreover, when a celloidin mass too thick to pass through capillaries was injected into the coronary arteries, celloidin plugs were found protruding from small openings in the endocardial walls of the atria and ventricles, while the capillary bed remained uninjected. From these experiments the conclusion was drawn that direct vascular communication existed between the coronary arteries and the heart chambers. F. H. Pratt⁷ has also observed plugs of gelatin protruding from the thebesian openings after injection of this thick mass into the coronary arteries. Mettier, Zschiesche, and Wearn⁸ in 1929, and Wearn, Klumpp, and Zschiesche⁹ in 1932 published the preliminary results of some experiments which are reported in full in this paper.

Grant and Viko¹⁰ in 1929 injected the thebesian vessels through their endocardial foramina and through the coronary vessels. They used finely drawn glass cannulas of such sizes as to fit snugly into the endocardial foramina. Their injection pressure was produced by blowing from the mouth into the injection system. By this means a pressure of about 50 to 60 mm. Hg was obtained. They were able to confirm the existence of anastomoses between thebesian vessels and coronary veins and described several types of venous anastomoses. They also injected the coronary arteries but failed to find evidence of direct arterial communications and concluded that "the coronary arteries communicate with the thebesian vessels only through capillaries."

Stella¹¹ in 1931 employed the denervated heart-lung preparation in dogs in an attempt to test the claim of the existence of communications between the arteries and heart cavities by a physiological method. He

was able to maintain the pressure within the ventricles and drop the pressure within the coronary arteries and, since under such conditions he was unable to demonstrate back-flow from the chambers into the arteries, he concluded that his work did not support the existence of large channels connecting the thebesian veins with the coronary arteries.

Grant¹² in 1926 found in a child's heart, which presented a congenital anomaly, persistent channels communicating freely with the heart cavities and with the coronary arteries, veins, and capillaries. Bellet, Gouley, and McMillan¹³ in 1933 reported dilated sinusoids or thebesian veins in a heart which showed an advanced tuberculous fibrocaseous infiltration.

In view of the lack of agreement on the existence of vascular connections between the coronary arteries and the heart chambers, the experiments reported in this paper were devised and carried out.

METHODS AND OBSERVATIONS

Human hearts obtained at necropsy were used in the experiments reported in this study. No effort was made to select normal or abnormal hearts. Hearts were accepted for injection whenever they could be obtained from the necropsy table. The causes of death covered a wide range, but it so happened that none of the hearts showed any gross evidence of any pathological process.

The use of thick celloidin as an injection mass offered a method of approach in determining the presence and constancy of arterial communications with the heart chambers. In a previous experiment⁶ it was found that celloidin could be prepared in a suspension sufficiently thin to pass through arteries and arterioles but too thick to penetrate the capillaries. The injection mass consisted of a 5 per cent solution of celloidin in acetone. A blue fluid mass was obtained by mixing crystal violet and brilliant green with the celloidin, and a red fluid mass was made by the addition of alkanin to the celloidin.¹⁴ The red celloidin mass was used in making a cast of the ventricular chambers, and the blue for casting the coronary arteries. The following experiment is a typical one and illustrates the method:

PROTOCOL

Heart 10. Male. Aged thirty-two years. Death was the result of staphylococcus septicemia. The heart was placed in the ice box for twenty-four hours to allow for the passing off of rigor mortis, following which it was gently massaged in warm salt solution to break the remaining rigor and to remove all blood clots in the chambers. The coronary sinus and the tricuspid valve were closed by purse-string sutures. (In some instances the valve leaflets were everted and clamped.) A cannula was tied into each coronary artery and into the pulmonary artery. The red celloidin mass was injected through the cannula in the pulmonary artery into the right ventricle at a pressure of 160 mm. Hg, and this pressure was maintained until the experiment was completed. At the same time, suction was applied to the



Fig. 1.



Fig. 2.

Plate I

Fig. 1.—Heart 10. The painting shows a red celloidin cast of the chamber of the right ventricle and a blue celloidin cast of the coronary arteries. The outer branches of the arteries have been removed in order to show the red tips at the junctions of the coronary arteries and the red cast of the chamber. The artery tips are firmly fused with the celloidin cast of the right ventricular cavity (see Protocol of Heart 10).

Fig. 2.—Heart 10. A painting on a larger scale to show more clearly the red tips at the points where the casts of the coronary artery fuse with the cast of the right ventricular cavity (see Protocol of Heart 10).

cannulas in the coronary arteries. After a lapse of ten minutes the suction was discontinued, care being taken to prevent the entrance of air, and the blue mass was injected into the coronary arteries at a pressure of 180 mm. Hg. This pressure was maintained for fifteen minutes, after which the cannulas were clamped off and the heart was plunged immediately into ice water where it remained for forty-eight hours to permit maceration of the muscle. The heart was then placed in 75 per cent HCl for seventy-two hours, during which time the acid was changed twice. This usually completed maceration of the muscle. The cast was washed free of muscle by playing a very fine stream of water on the débris. (Extreme care was necessary in this procedure to avoid breakage of the finer vessels.) After washing, the cast was mounted.

A reproduction of a painting of this specimen is shown in Plate I, Figs. 1 and 2, and a photograph of the same specimen in Plate II, Fig. 1. The specimen consists of a solid red cast of the chamber of the right ventricle and blue casts of the anterior branches of the right and left coronary arteries. It is to be noted that some of the terminations of the branches of the anterior branch of the right coronary artery are red in color. These red tips vary from 4 to 15 mm. in length. The distal ends are continuous with the red mass in the ventricles, and the proximal ends fuse smoothly with the blue mass in the arteries. Such vessels when grasped between the fingers or with forceps are found to be firmly attached by this red tip to the ventricular mass, showing complete fusion of the two celloidin masses. The cast of the vessels is smooth and round and shows no lateral communications. Capillaries are not injected. It is evident, therefore, that the red celloidin mass has found its way directly from the right ventricle into the terminations of the right coronary artery, as shown by its fusion with the blue mass injected into the artery at its origin. The pressure within the right ventricle probably aided in the entrance of the red mass into the ends of the branches of the coronary arteries.

Fifteen human hearts were injected according to the technic described in the preceding protocol. In all of the final specimens red tipped terminations of arteries fused to the ventricular mass were found. The number of these vessels in each heart varied with the completeness of the injection and with the degree of damage that occurred during the washing process. A composite of all of the specimens injected would average about twenty to twenty-five communicating arteries scattered generally over the heart walls. It is not felt that these figures represent the total number of communications, for in many instances it was obvious that the injection was incomplete.

These communicating vessels between the coronary arteries and the ventricles usually had their origin from the main trunks of the coronary arteries during their course toward the apex of the heart. Many of the deeper branches of the arteries lying near the endocardium also gave off frequent branches. As many as eight to ten communicating branches were frequently seen in the course of the anterior branch of the left

Fig. 1.



Fig. 2.

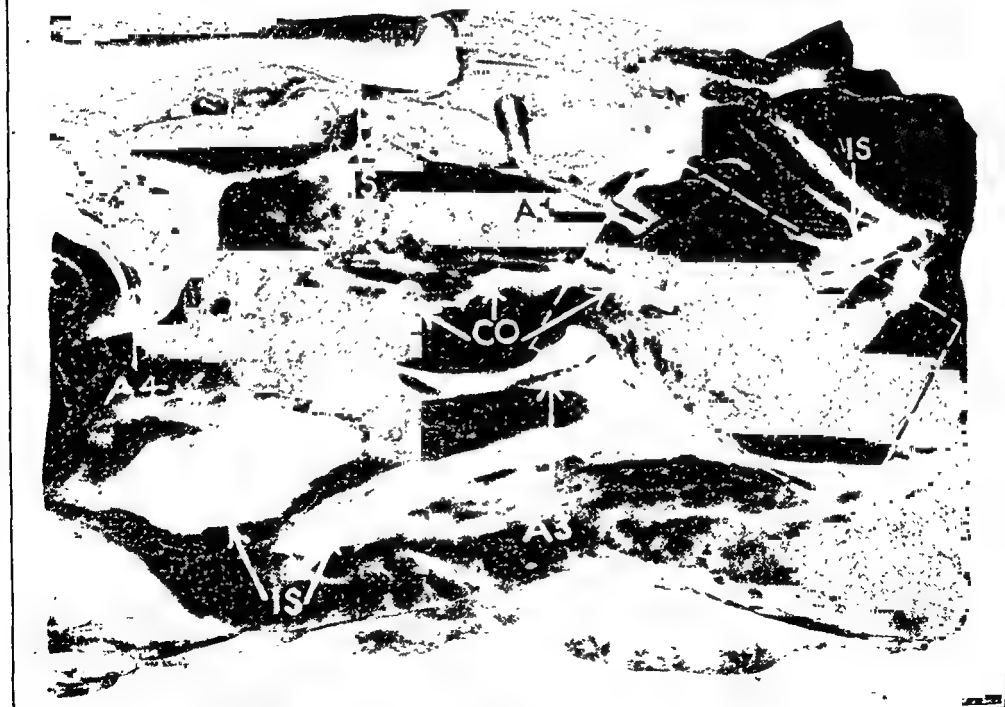


Fig. 3.

Plate II.

Fig. 1.—Heart 10. A photograph of the same specimen shown in the painting in Plate I, Figs. 1 and 2.

Fig. 2.—Heart 9. A celloidin cast of the right ventricular chamber and the coronary arteries. It shows firm fusion of the tips of some of the arteries with the cast of the chamber.

(See opposite page for explanation of Fig. 3.)

coronary artery from the base to the apex, and several openings were usually found near the apex of the ventricles. In one specimen in which both ventricles were injected, communicating vessels passed from the left anterior coronary artery to both chambers. From six to eight vessels were found with great regularity in the upper two-thirds of the anterolateral surface of the right ventricle. They have not been demonstrated with as great a frequency on the posterior surface of the heart, but in one well-injected specimen there were six entering the right ventricle posteriorly. Many of these vessels terminated not only on the surface of the columnae carneae, as represented by the depressions in Plate I, Figs. 1 and 2, and in Plate II, Fig. 1, but in the intercolumnar spaces as well.

In order to determine the relation of the arterial terminations to those of the veins a heart was prepared in the following manner:

PROTOCOL

Heart 11. Male. Aged thirty-four years. Died of pneumonia. The heart was placed in the ice box for forty-eight hours and then washed and massaged in the usual manner. A cannula was tied into each coronary artery; one in the pulmonary artery and one in the coronary sinus. The tricuspid valve was closed and made water-tight with an Ochsner clamp. A red celloidin mass was injected into the right ventricle at a pressure of 160 mm. Hg and suction was applied to the cannulas in the coronary arteries and in the coronary sinus. After fifteen minutes the suction apparatus was removed in such a manner as to prevent the entrance of air, and the blue mass was injected into the arteries and into the coronary sinus. Some of the dye escaped from the veins into the atria. Pressure was released at the end of fifteen minutes and the heart was plunged into ice water. The specimen was macerated and mounted by the technic described in the preceding protocol.

The specimen consisted of a solid red celloidin cast of the chamber of the right ventricle. Study of this specimen showed not only the red tips to the arteries as previously described, but in addition, several small red tips to the veins which were firmly fused with the blue mass in the veins, thus providing direct evidence of venous communication with the ventricular chambers. This finding of venous connections with the ventricles was in agreement with former work⁶ in which serial sections demonstrated direct communication between thebesian vessels and the coronary veins.

The evidence for the existence of communicating vessels between the coronary arteries and the heart chambers in fifteen consecutive hearts

Plate II (Continued). Fig. 3.—Heart 23 Kb. A photograph of a wax-plate reconstruction of a section of the left ventricular wall near the apex, in which is shown the common opening (CO) through which several "arterio-luminal" vessels and "myocardial sinusoids" open into the lumen of the ventricle. Several intertrabecular spaces (IS) are shown. The wax has been dissected away to show the arteries (A₁, A₃, and A₄) which communicate with the cavity through the common opening. The dotted rectangle includes the tissue from which serial sections shown in Plate III, Fig. 2, and Plates IV, V, and VI were cut. Structures shown in this figure and in Plates III, IV, V, and VI are from the same heart and are designated identically for comparison. This photograph has been reduced to approximately three-fifths of the size of the original model which was constructed on a magnification of 20 times the original block of tissue.

seemed conclusive. Vieussens¹ called these vessels "*vaisseaux charnus*" or fleshy vessels. His reason for so designating them, however, was based upon a misconception. He believed that the myocardium was made up of vessels springing from the coronary arteries "as hairs from a wig" and he made no distinction between the vessels and the muscle fibers. For the sake of clarity and to avoid confusion, this group of vessels will henceforth be referred to in this paper as "arterio-luminal" vessels. This term is suggested inasmuch as they run from the coronary arteries into the lumen of the heart. For those connecting vessels between the coronary arteries and the atria the term "arterio-atrial" vessels might be used, and similarly for those between the coronary arteries and the ventricular chambers the term "arterio-ventricular" vessels might be employed.

Inasmuch as the structure of such vessels had never been described, the next step in the study was obvious. Moreover, it was felt that, if one of these vessels could be identified in the intact heart wall, a block of tissue containing it could be removed, sectioned serially and reconstructed. Such a study, if carried out successfully, should answer the possible criticisms that the connections shown in the celloidin casts were due to artifacts. In addition, it should establish beyond question the arterial origin of the communications and reveal the histological structure of the vessels themselves.

In approaching this task, several difficulties were encountered which necessitated a change in the injection mass employed. It was a simple matter to identify the celloidin plugs protruding from the openings of the "arterio-ventricular" communicating vessels, but, in the course of fixation, dehydration, mounting, and staining, the celloidin was dissolved and the vessels could not be traced. In order to overcome this difficulty, a suspension of Berlin blue in gelatin* was selected as an injection mass. A few experiments revealed, however, that this mass penetrated the capillaries and thus made it extremely difficult to follow the "arterio-luminal" communicating vessels. A method had to be devised, therefore, which would keep the gelatin from entering the capillaries. It was necessary of course to carry out the gelatin injections at a temperature slightly above the solidifying point of gelatin. This was accomplished by immersing the heart, injection bottle, and connecting tubing in a tank of water at the proper temperature. It was found that the introduction of cold salt solution into the ventricles at the appropriate time caused a chilling of the myocardium which allowed the gelatin to flow through the arteries and arterioles but aided in the prevention of its entrance into the capillaries. Under such conditions, it

*The injection mass was made up as follows: Soak 100 grams of Silver Label gelatin (Michigan Carbon Works) for two hours in 150 c.c. of distilled water. Warm over a water-bath until the gelatin dissolves, then add 5 grams of Berlin blue suspended in 100 c.c. of distilled water and thoroughly mix. Add 1 gram of thymol and filter the mass through several thicknesses of gauze.

was possible to inject the "arterio-luminal" communicating vessels without filling the capillary bed. When the heart was opened, solid gelatin plugs were found protruding from the endocardial openings of the channels, the gelatin having solidified on contact with the chilled salt solution in the ventricular cavities.

A block of heart muscle containing the opening, from which the gelatin protruded, was excised and placed under a binocular bi-objective dissecting microscope where the opening was identified and marked with India ink. The tissue block was then fixed and imbedded in paraffin preparatory to cutting serial sections. The following protocol illustrates the method:

PROTOCOL

Heart 23 Kb. Aged thirty-five years. Death resulted from lobar pneumonia. Heart weight 440 gm. (This weight was recorded before large clots were removed from the cavities.) This experiment was started forty hours post-mortem. Blood clots were removed from the ventricles so far as was possible. The coronary sinus and posterior great veins were tied off near their entrance to the right atrium. The coronary arteries were cannulated. Rubber tubing was led into the left and right ventricles through the aorta and the pulmonary artery respectively for the purpose of introducing chilled salt solution into these cavities. The aorta and pulmonary artery were closed by filling the space around the rubber tubing with cotton. The atrio-ventricular valves were then closed by placing cotton pledgets in their openings. These steps were taken in order to seal the ventricular chambers, thereby preventing the entrance into them of gelatin from any source other than from the openings in their own walls. The coronary cannulas and the rubber tubing connecting them with the bottle of injection mass were warmed and filled with gelatin after the removal of all air. The heart and injection apparatus were then placed in a water-bath at a temperature of 25° C. preparatory to starting the injection. The temperature of the gelatin was 53° C. Physiological salt solution chilled to a temperature of -2° C. was introduced into the ventricles in sufficient quantity to fill the chambers. After a lapse of approximately one or two minutes, the injection of Berlin blue gelatin into the coronary arteries was begun. The flow soon ceased but the injection pressure of 220 mm. Hg was maintained for about five minutes.

After sufficient time had elapsed to allow for solidification of the gelatin, the heart was opened with great care in order to prevent the entrance of any gelatin from the outside. The cotton pledgets in the atrio-ventricular valves, as well as those in the aorta and pulmonary artery, were inspected and removed. No leakage of gelatin into the ventricles had occurred.

Inspection of the myocardium showed an excellent injection of the main arteries and arterioles. That part of the heart muscle which received most of its blood supply from the left coronary artery showed some capillary injection immediately beneath the pericardium where the muscle had not been chilled. There was no evidence of capillary injection in the muscle supplied mostly by the right coronary artery.

Blocks of the heart wall showing gelatin protruding from the endocardial openings were removed from the following positions for study:

1. Right ventricle: Septal wall, halfway between pulmonary valve and apex.
2. Left ventricle: At the apex from a pocket formed by the junction of two trabeculae. (It is from this tissue that the reconstructions shown in Plate II, Fig. 3, and Plate III, Fig. 1 were made.)

The tissue removed from the left ventricle in the experiment just described was fixed, imbedded in paraffin, cut into serial sections eight micra thick, mounted and stained with van Gieson's stain. Careful study of these sections revealed convincing evidence of direct communications between the coronary arteries and the chambers of the ventricles.

Inasmuch as these communicating channels frequently ran through many of the histological sections, it was obviously impossible to publish photographs of all the sections. All sections were cut eight micra thick and for this reason sharp photomicrographs could not be obtained in each instance. It was felt, therefore, that the vessels should be reconstructed, inasmuch as such a procedure would submit our microscopic observations to a further test of accuracy. In carrying out the reconstruction, it was our good fortune to have the constant guidance and criticism of Dr. Bradley M. Patten of the Department of Histology in the School of Medicine of Western Reserve University. Dr. Patten's wide experience in this field made his advice and help invaluable.

A reconstruction in wax (Plate II, Fig. 3) was made of the block of myocardium according to the Born wax-plate reconstruction method in order to show the gross relationship of the arteries to the common opening* in the endocardium and to determine whether the common opening, into which the communicating vessels opened, connected with other intertrabecular spaces. This model was constructed on a scale twenty times the size of the original block of tissue. Its purpose was to show only gross relationships which might serve as guides in the construction of a second model of greater magnification. The wax has been dissected away in order to bring the arteries into view. Reference to the figure (Plate II, Fig. 3) will show three arteries lying in close proximity to the common opening from which the gelatin plug protruded before its removal in the process of imbedding. Branches from all three of the arteries shown opened into the common opening, and the common opening itself was found to communicate with three other intertrabecular spaces shown in the model. The lettering of the structures in the figure (Plate II, Fig. 3) is identical with that used for all other plates of the same heart (H 23 Kb) and is so arranged that the same structure is designated by the same letter in Plates III, IV, V, and VI. For instance, A₁ represents the same artery in each of these plates.

*The term "common opening" is used in the sense that Vieussens used it, namely, to indicate an inpocketing of the endocardium into which several vessels opened.

Plate III. Fig. 1.—Heart 23 Kb. Photograph of a wax-plate reconstruction of the "arteriosinuosidal" vessels and the "myocardial sinusoids" in the block of tissue shown within the broken lines in Plate II, Fig. 3. The structures shown in the model represent reconstructions of the lumina of the vessels. For instance, A₁ is an artery, AS₁ is a branch of the artery which empties directly into the common opening (CO) which is an inpocketing of the endocardium of the left ventricle. A₁ and CO, for instance, are shown in Plate II, Fig. 3, and are labeled identically. This wax-plate reconstruction was made on a scale of 200 times the original. This photograph is approximately one-fifth of the actual size of the model.

Fig. 2.—Heart 23 Kb. A photograph of one of the serial sections from which the model in Fig. 1 of this plate was reconstructed. The various structures in this figure are designated identically with those in Fig. 1. END = endocardium. MS = "myocardial sinusoid." CO = common opening. AS = "arterio-sinusoidal" vessel. A = artery. OMS = opening of a "myocardial sinusoid" into the lumen of the ventricle. Numbers appearing after letters enable one to identify the same structures in Plate II, Fig. 3, and Plates III, IV, V, and VI. (X41)

Fig. 1.

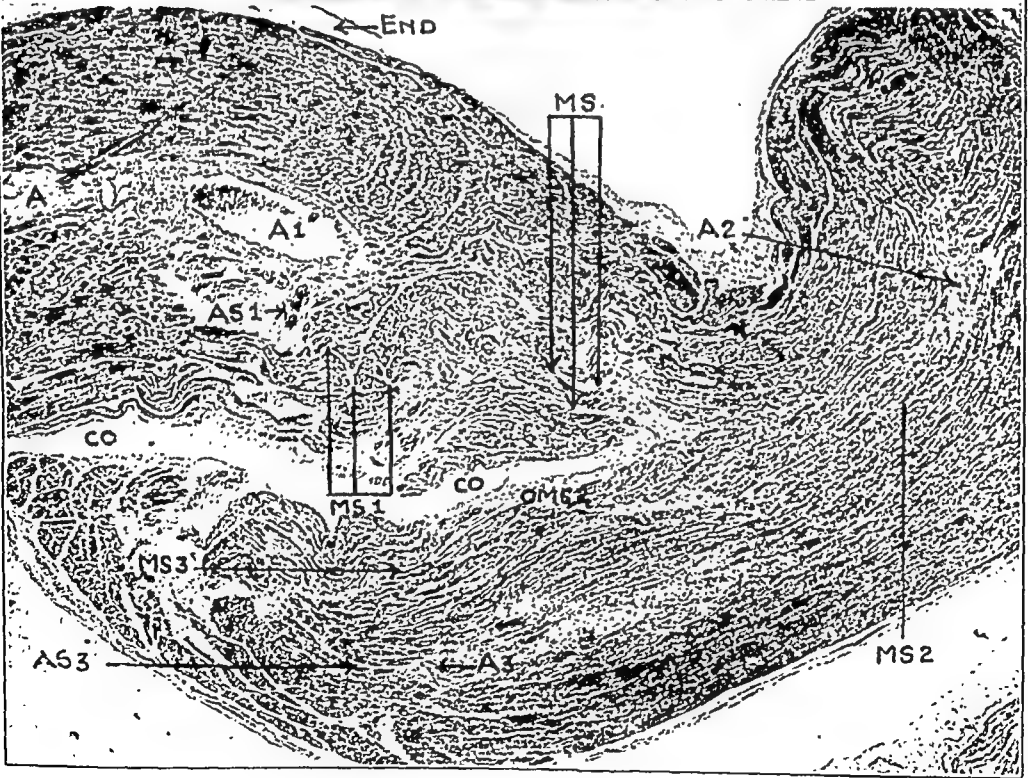
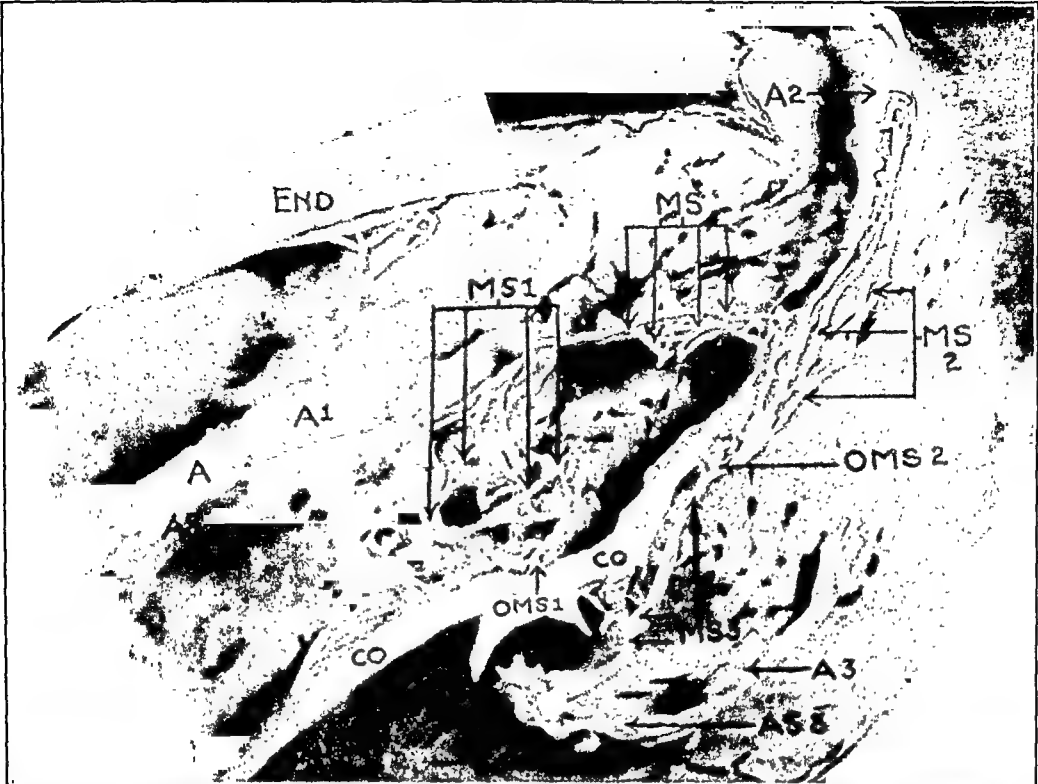


Fig. 2.

Plate III.

(See opposite page for explanation of Figs. 1 and 2.)

In one particular part of the block of myocardium which was used in making the serial sections, a number of arterial branches were found which communicated with the lumen of the ventricle via the common opening. This area is indicated by the dotted rectangle in Plate II, Fig. 3. It was found that several communicating vessels lay within this small space; consequently, it was selected for a second reconstruction. In carrying out this reconstruction, the lumina of the blood vessels and of the intertrabecular space were reconstructed so that in the final state the model represented a cast of the cavities of the blood vessels and their openings into the lumen of the ventricle through a common opening. The drawings used in the reconstruction of this model were made from projections of the individual sections at a magnification of 200 diameters. Plate III, Fig. 2 is a low power photomicrograph of one of the sections used in the reconstruction of the model shown in Plate III, Fig. 1.

Completion of the model of the vessels furnished confirmation for our microscopic observations. Moreover, the careful study of the sections which was necessary for accurate reconstruction brought to light two distinct groups of vessels which serve as communicating channels between the arteries and the heart chambers. A vessel of the first group is usually a small branch of a coronary artery which gradually loses its arterial character through changes in its wall due to the loss of the media, thinning of the intima, and a gradual disappearance of the adventitia. Such a vessel breaks up into channels whose lumina are very irregular. The walls of these channels are very thin and are made up of endothelium only or of endothelium reinforced by a minimal amount of subendothelial connective tissue. The diameters of these channels may vary from 50 to 250 micra. The characteristics of these vessels are identical with those of sinusoids as described by Minot¹⁵ in 1900. Their walls lie in close contact with the heart muscle, running between bundles of muscle fibers and at times between the fibers themselves. Hereafter, in this paper these channels will be referred to as "myocardial sinusoids." The arterial branches which supply the sinusoids will be referred to as the "arterio-sinusoidal" vessels. Such a name indicates the origin and the distribution of the vessels. An "arterio-sinusoidal" vessel is shown in Plate V, Figs. 1, 2, 3, and 4. A "myocardial sinusoid" is also shown in Plate V, Figs. 4 and 5. The fact that the wall of the "arterio-sinusoidal" vessel is arterial in character at the beginning and gradually changes to that of a simple endothelial tube of irregular lumen and diameter makes it inadvisable to call it either artery or vein. It can be differentiated with ease from

Plate IV. Fig. 1.—Heart 23 Kb, section 139. The branching of the artery (A_1) is shown. The branch (AS_1) divides into "myocardial sinusoids" (MS_1) which empty into the common opening (CO) at (OMS_1). See Fig. 2. ($\times 361$)

Fig. 2.—Heart 23 Kb, section 142. Shows the opening of the "myocardial sinusoid" (MS_1) into the common opening (CO). ($\times 340$)

Fig. 3.—Heart 23 Kb, section 137. Shows a section of the "arterio-sinusoidal" vessel (AS_1). The wall of the artery (A_1) from which it arises is shown.

Fig. 1.

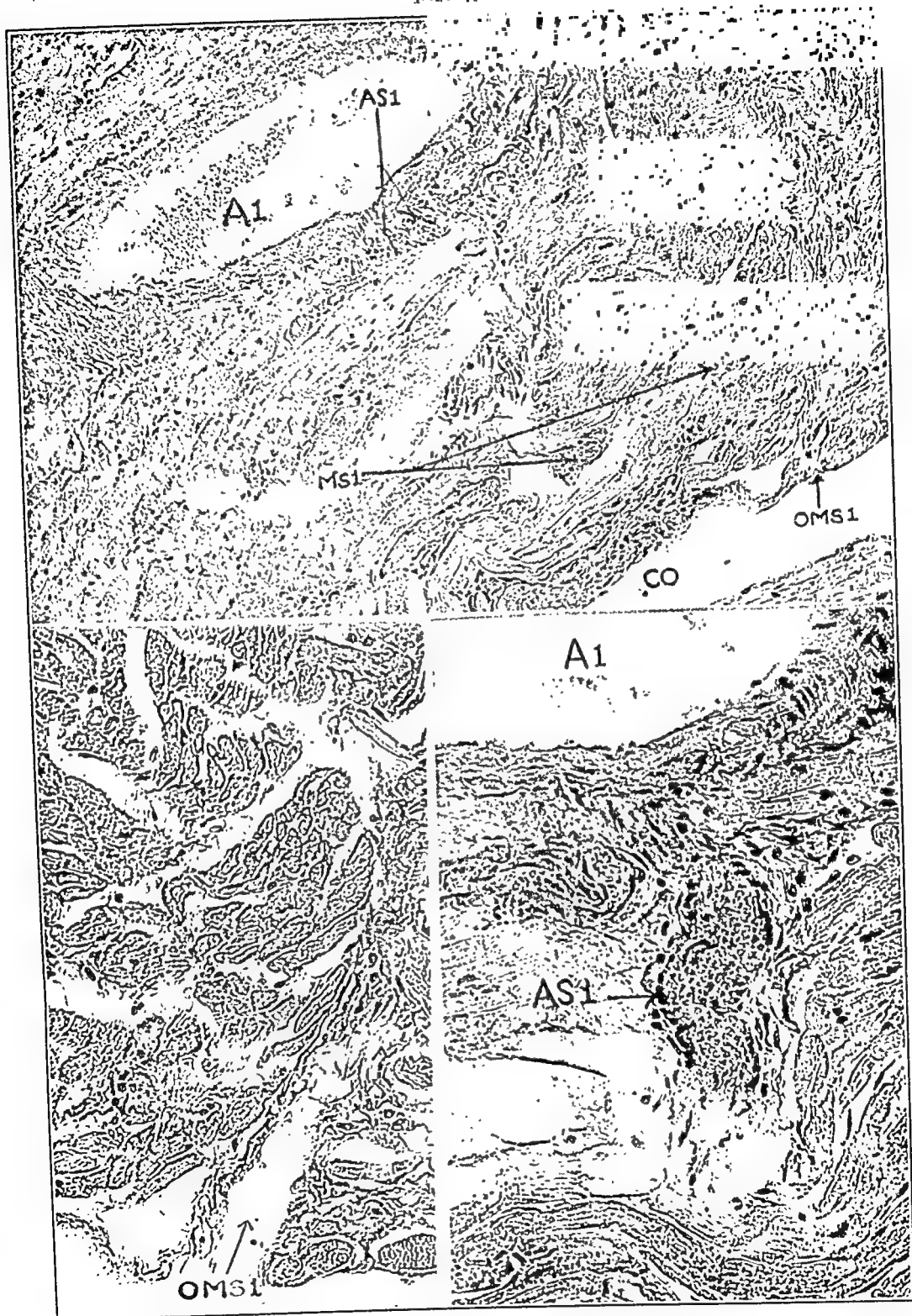


Fig. 2.

Fig. 3.

Plate IV.

(See opposite page for explanation of Figs. 1, 2, and 3.)

a capillary by its much greater diameter and by its irregular lumen. The "arterio-sinusoidal" vessels may lose their arterial character immediately after branching from the artery (Plate V, Figs. 3 and 4). At times these vessels may give off a branch which divides into capillaries.

The "myocardial sinusoids" run a meandering course, anastomose very freely with one another and not infrequently with capillaries, and open into the lumen of the ventricle either directly or through a common opening. The model (Plate III, Fig. 1) illustrates the origin of the "arterio-sinusoidal" vessels. It also shows the anastomosing "myocardial sinusoids" and their openings into the common opening which is a simple inpocketing of the endocardium (Plate III, Fig. 1). In some instances, the "myocardial sinusoids" may run a direct course from the "arterio-sinusoidal" vessel to the lumen of the ventricle. (See Plate III, Fig. 1, A2 and MS2, and Plate VI, Figs. 1 and 2.)

When closed and empty, the "myocardial sinusoids" resemble closely and are easily mistaken for strands of fibrous tissue. One frequently finds a "myocardial sinusoid" cut longitudinally with small pockets of erythrocytes here and there to identify it as a vessel. Between the pockets of erythrocytes the walls may lie against one another and resemble somewhat similar structures in the bone marrow.

The similarity of the walls of the "myocardial sinusoids" to those of capillaries and the somewhat similar distribution between, and in close contact with, muscle bundles and muscle fibers would indicate that the "myocardial sinusoids" play a definite rôle in supplying parts of the heart with blood.

The second type of communicating vessels observed ran much more directly from the coronary arteries to the lumen of the ventricle. These vessels were similar to and undoubtedly identical with the "arterio-luminal" vessels described earlier in this paper and reproduced in Plate I, Figs. 1 and 2, and Plate II, Figs. 1 and 2. The finding and identifying of the "arterio-luminal" vessels by histological methods and the tracing of their course from the artery to the heart lumen by reconstruction are confirmatory of the experiments in which celloidin injections were employed and which were described earlier in this report. Two photomicrographs of "arterio-luminal" vessels are shown in Plate

Plate V. Fig. 1.—Heart 23 Kb. section 183. Shows the branching of an "arterio-sinusoidal" vessel (AS_1) from an artery (A_1). ($\times 410$)

Fig. 2.—Heart 23 Kb. section 180. Shows the artery (A_1) and the "arterio-sinusoidal" vessel (AS_1). Note the thickness of the wall. ($\times 372$)

Fig. 3.—Heart 23 Kb. section 152. Shows the artery (A_1) at the extreme right edge of the figure and the "arterio-sinusoidal" vessel which has divided (AS_1) at the left. ($\times 270$)

Fig. 4.—Heart 23 Kb. section 137. Shows the "arterio-sinusoidal" vessel (AS_1) with the wall much thinner. At the right of the section a "myocardial sinusoid" (MS_1) is shown. ($\times 410$)

Fig. 5.—Heart 23 Kb. section 133. Shows the "myocardial sinusoid" (MS_1) into which the "arterio-sinusoidal" vessel (AS_1) opened. ($\times 410$)

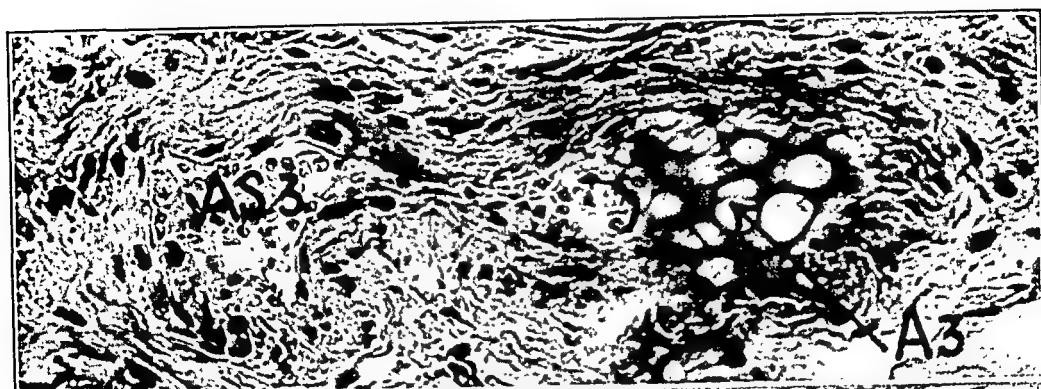


Fig. 1.

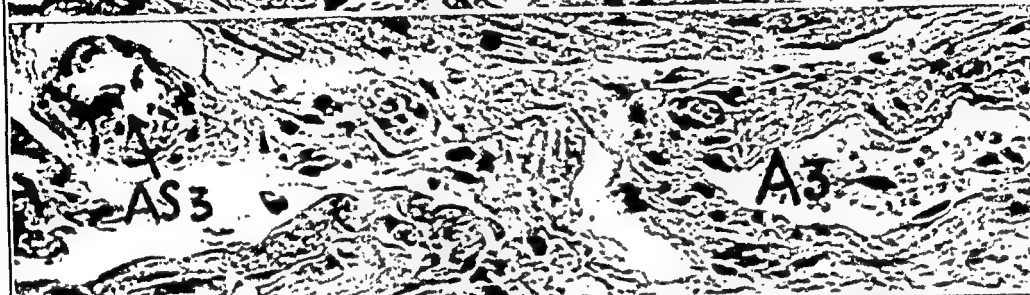


Fig. 2.

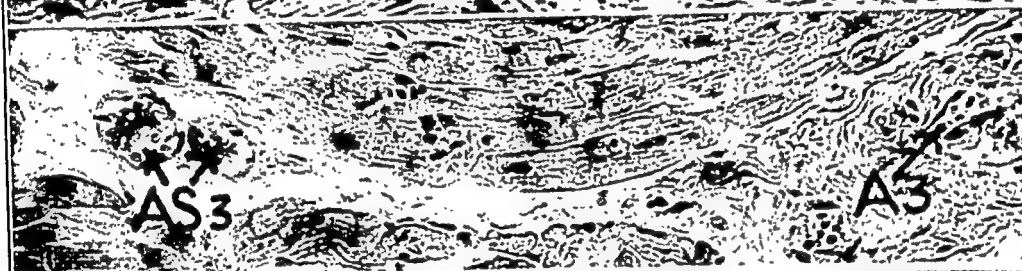


Fig. 3.



Fig. 4.



Fig. 5.

Plate V.

Several successive stages of an "arterio-sinusoidal" vessel (AS_3) are shown. The change in the wall from the point at which it leaves the artery (A_3) to the loss of its wall upon becoming a "myocardial sinusoid" is illustrated.

(See opposite page for explanation of Figs. 1-5.)

VII, Figs. 2 and 3, and Plate VIII, Figs. 1, 2, 3, and 4. These vessels usually run a direct, short course from the artery to the heart cavity. Even in their relatively short course, however, some of these vessels give off branches which break up into capillaries.

The walls of these vessels are thicker than those of the "arterio-sinusoidal" vessels and they retain their thickness almost to the point of entrance of the vessels into the heart cavity. At times, however, they lose their thick walls immediately after branching from the parent artery. The actual thickness of the walls or the actual diameter of the lumina is difficult to measure, since none of these vessels was found with its lumen completely filled or distended. Several diameters of vessels in the collapsed state were measured and ranged from 0.04 mm. to 0.2 mm. The diameters of the "arterio-luminal" vessels as estimated from the celloidin cast (Plate II, Fig. 1) ranged from 0.2 mm. to 1.0 mm.

The "arterio-luminal" branches of the coronary arteries were found to communicate with the atria and ventricles. They appeared to be more numerous in the ventricles than in the atria.

In view of the fact that the large number of "arterio-sinusoidal" branches and "arterio-luminal" vessels just described were observed in one small block of myocardium, a search was started for similar vessels in other hearts which had been injected by various methods.⁶ The search was soon rewarded, for in the first two hearts studied "arterio-sinusoidal" vessels were found and the "myocardial sinusoids" were easily recognized. In the third and fourth hearts studied, several "arterio-luminal" vessels were discovered (Plate VII, Figs. 2 and 3, and Plate VIII, Figs. 1, 2, 3, and 4). In five consecutive human hearts studied, therefore, "arterio-luminal" or "arterio-sinusoidal" vessels were found. Inasmuch as the "myocardial sinusoids" open into the lumen of the ventricle, it follows that in tissue from five consecutive hearts from which serial sections had been prepared direct vascular communications between the coronary arteries and the heart chambers were observed.

Recent contributions have shown that the coronary circulation is not limited to the common order of vessels—artery, capillary, and vein—but is safeguarded by other channels which offer collateral routes for the blood stream. The thebesian veins, for instance, have been shown^{5, 6, 10, 16} to communicate with the cardiac veins, with the capillaries, and with

Plate VI. Fig. 1.—Heart 23 Kb. section 139. Shows artery (A_2) from which an "arterio-sinusoidal" vessel (AS_2) has just branched. The "arterio-sinusoidal" vessel (AS_2) opens into the "myocardial sinusoid" (MS_2). ($\times 360$)

Fig. 2.—Heart 23 Kb. section 139. Shows the same "myocardial sinusoid" (MS_2) as shown in Fig. 1 as it approaches the ventricular cavity via the common opening (CO). The actual opening, while not shown in this section, is in the region labeled OMS₂. At the top of the figure can be seen a closed "myocardial sinusoid" (CMS). Note the fact that MS_2 is also closed in places. ($\times 360$)

Fig. 1.



Fig. 2.
Plate VI.

(See opposite page for explanation.)

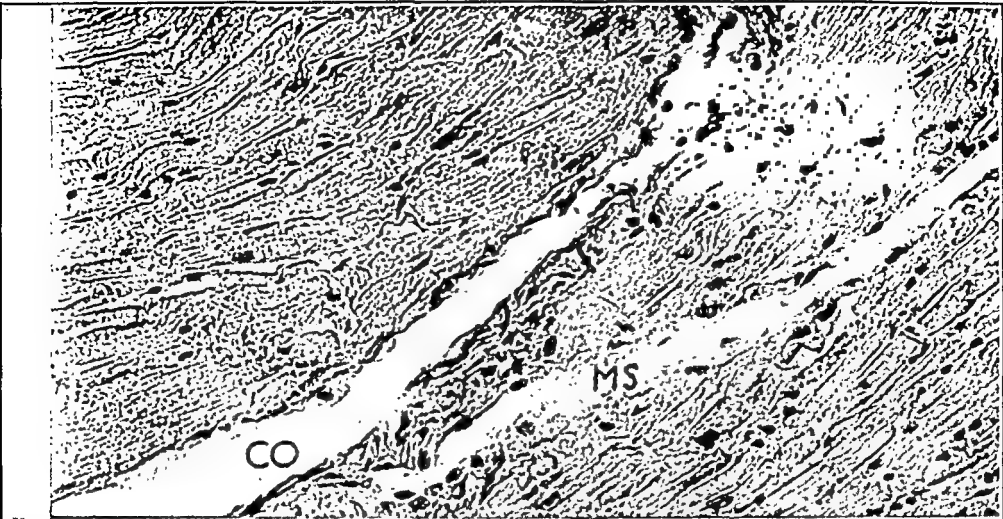


Fig. 1.

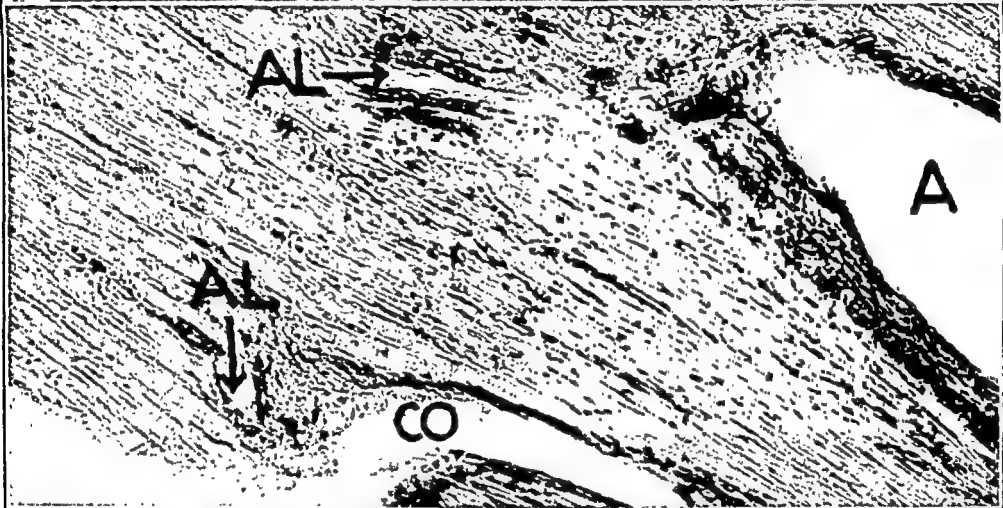


Fig. 2.

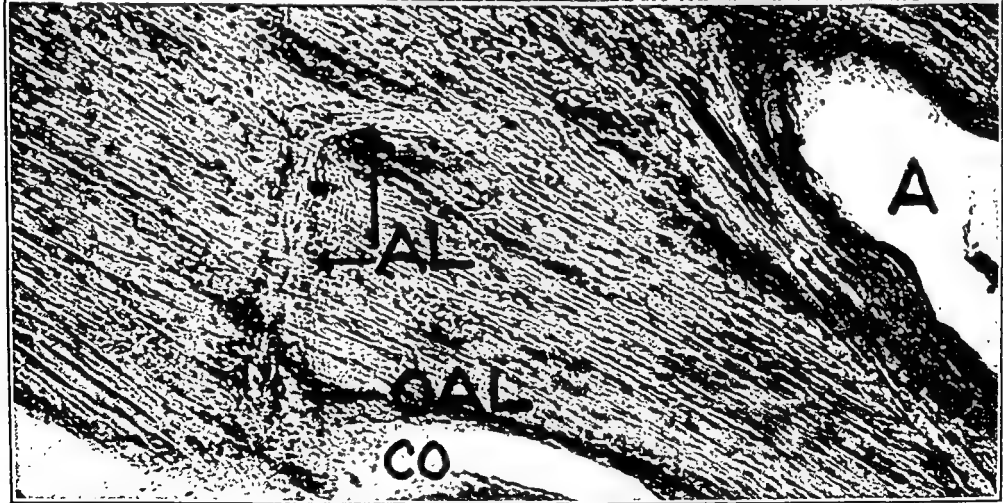


Fig. 3.

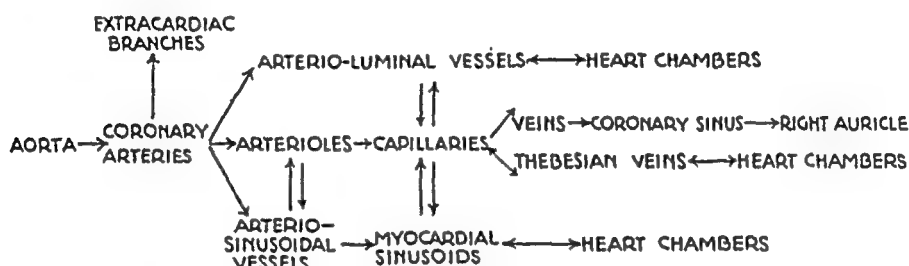
Plate VII.

Fig. 1.—Heart 23 Kb, section 142. Shows a “myocardial sinusoid” (MS) approaching the common opening (CO). (X340)

Fig. 2.—Heart 52. Shows an “arterio-luminal” vessel (AL) branching from the artery (A) and approaching the common opening (CO). Note the wall of the “arterio-luminal” vessel. (X158)

(See opposite page for further explanation of Plate VII.)

one another. More recently Hudson, Moritz, and Wearn¹⁷ have demonstrated extensive extracardiac anastomoses of the coronary arteries which extend into the mediastinum, lungs, parietal pericardium, both surfaces of the diaphragm, and through the vasa vasorum to the abdominal aorta. The evidence presented in this paper gives additional support to the claim made by Wearn⁶ in 1928; namely, that direct vascular communications other than capillaries exist between the coronary arteries and the chambers of the heart. If these various vascular channels are introduced into the scheme of the coronary circulation, it can be set up in a diagrammatic fashion as follows:



Blood entering the coronary arteries, therefore, has a possible exit through any one or all of four routes:

1. By extracardiac anastomoses;
2. By way of the capillaries and veins
 - (a) into the coronary sinus or great cardiac veins and thence into the right atrium, or
 - (b) through the thebesian veins into the heart chambers;
3. By way of the "arterio-luminal" vessels directly into the heart chambers; and
4. By way of the "arterio-sinusoidal" vessels through the "myocardial sinusoids" into the chambers.

The last three systems also anastomose with one another. This structural diagram is proposed in order to indicate the arrangement of the vessels and not to show the direction of the flow within them.

A somewhat similar diagram of the circulation was published by Wearn⁶ in 1928, in which evidence of vascular connections between the coronary arteries and the heart chambers was presented. Inasmuch as the findings were based upon anatomical studies, no definite conclusions were drawn as to the function of the "arterio-luminal" vessels. No

Plate VII (Continued). Fig. 3.—Heart 52. Shows the artery (A) and the "arterio-luminal" vessel (AL) which empties into the common opening (CO) at (OAL). (X158)

Figs. 2 and 3 are photographs of consecutive serial sections. A = artery. AL = "arterio-luminal" vessel. OAL = opening of "arterio-luminal" vessel into the lumen of the ventricle.

claim was made that the coronary capillaries were perfused during systole as quoted by Stella,¹¹ but certain speculations were indulged in which have led him to enter the field and search for the "arterio-luminal" vessels by means of a physiological method. Employing the denervated heart-lung preparation, he attempted to establish back-flow from the ventricles into the coronary arteries. Under the conditions of his experiment, the heart would beat for "one or two minutes" before beginning to fail. During these two-minute periods he was unable to establish back-flow from the chambers to the arteries and, therefore, concluded that channels between them did not exist. His results are not surprising, for it was pointed out in 1928⁶ and emphasized by Leary and Wearn¹⁸ in 1930 that, if sufficient time were allowed, the thebesian—and this should now include the "arterio-sinusoidal" vessels and the "myocardial sinusoids"—could substitute for the coronary arteries in supplying blood to the myocardium. Stella's failure to reverse the normal direction of flow and establish a back-flow in a failing heart within two minutes seems to us to have little, if any, bearing upon the existence of vascular channels between the coronary arteries and the heart chambers. Such negative evidence certainly cannot be admitted as proof that such channels do not exist.

The failure of Grant and Viko¹⁰ to find communicating vessels between the arteries and the heart chambers led them to deny their existence. The methods employed by these workers were probably to blame for their failure. The common openings, into which the "arterio-luminal" vessels and "myocardial sinusoids" open, frequently communicate freely with the intertrabecular spaces, and this fact alone would render injection from the endocardial end almost impossible. Moreover, the openings of the "arterio-luminal" vessels usually lie deeply concealed in the intertrabecular spaces; and it is possible that Grant and Viko injected only the thebesian veins and did not find any of the "arterio-luminal" openings.

In our hands, many failures were experienced at first in attempting to inject the communicating vessels with celloidin and gelatin. The celloidin frequently solidified upon coming into contact with fluid in the arteries. The failure with the gelatin injections could be traced usually to improper temperature regulation. Careful control of these factors led to the successful injections.

Plate VIII. Fig. 1.—Heart 9B. Injection mass India ink. At the right of the figure is an artery (A) of which the "arterio-luminal" vessel (AL) is a branch. At the extreme upper left of the figure may be seen the common opening (CO). (X64)

Fig. 2.—Heart 9B. Shows a higher magnification of the "arterio-luminal" vessel (AL) and the common opening (CO) shown at the left of Fig. 1.

Figs. 2, 3, and 4 are consecutive serial sections, showing the "arterio-luminal" vessel (AL) as it approaches the common opening (CO) and then enters it at (OAL) in Fig. 4. Each figure (X247).

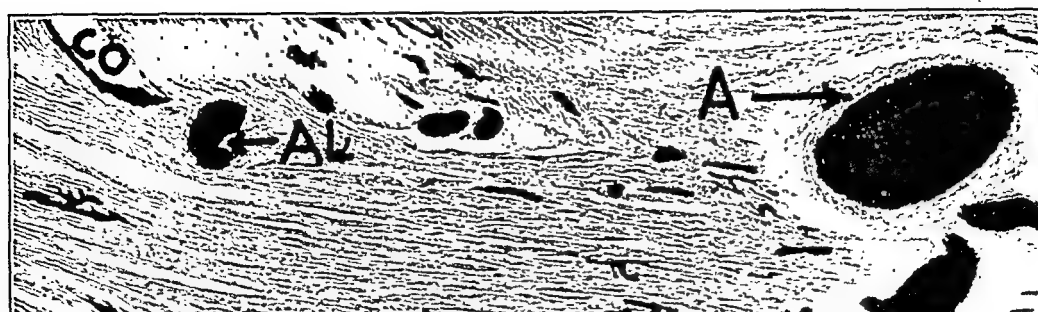


Fig. 1.



Fig. 2.



Fig. 3.



Fig. 4

Plate VIII.
 (See opposite page for explanation of Plate VIII.)

SUMMARY

By the employment of injection methods, it has been possible to demonstrate vascular communications between the coronary arteries and the chambers of the heart. Serial sections and wax-plate reconstructions of these communicating vessels revealed two types which have not been described previously. The first of these communicating vessels are small branches of arteries or arterioles lying near the endocardium. They run a short course and empty directly into the lumen of the heart and, for this reason, they have been referred to as "arterio-luminal" vessels. The second type of vessel arises as a branch of an artery or arteriole and soon breaks up into sinusoids which lie between the muscle bundles and at times between the individual muscle fibers. These vessels have been referred to as "arterio-sinusoidal" vessels, and the sinusoids have been designated as "myocardial sinusoids."

The histological structure of the "myocardial sinusoids" would indicate that they play a rôle in the nourishment of the heart muscle.

It is a pleasure to express our thanks to Dr. Alan R. Moritz for his most valuable assistance in taking the photomicrographs and also for his helpful criticisms.

REFERENCES

1. Vieussens, R.: *Nouvelles découvertes sur le coeur*, Paris, 1706.
2. Thebesius, A. C.: *Disputatio medica de circulo sanguinis in corde*, Lugduni Batavorum, 1708.
3. Lancisi, G. M.: *De motu cordis et aneurysmatibus (opus postumum)*, Lugduni Batavorum, 1740.
4. Abernethy, J.: *Phil. Trans. Royal Soc., London* 88: 103, 1798.
5. Pratt, F. H.: *Am. J. Physiol.* 1: 86, 1898.
6. Wearn, J. T.: *J. Exper. Med.* 47: 293, 1928.
7. Pratt, F. H.: *Personal communication*.
8. Mettier, S. R., Zschiesche, L. J., and Wearn, J. T.: *Trans. A. Am. Physicians* 44: 345, 1929.
9. Wearn, J. T., Klumpp, T. G., and Zschiesche, L. J.: *J. Clin. Investigation* 11: 823, 1932.
10. Grant, R. T., and Viko, L. E.: *Heart* 15: 103, 1929.
11. Stella, G.: *J. Physiol.* 73: 36, 1931.
12. Grant, R. T.: *Heart* 13: 273, 1926.
13. Bellet, S., Gouley, B. A., and McMillan, T. M.: *Arch. Int. Med.* 51: 112, 1933.
14. Hinman, F., Morison, D. M., and Lee-Brown, R. K.: *J. A. M. A.* 81: 177, 1923.
15. Minot, C. S.: *Proc. Boston Soc. Natural Hist.* 29: 185, 1900.
16. Kretz, J.: *Virchow's Arch. path. Anat.* 266: 647, 1927.
17. Hudson, C. L., Moritz, A. R., and Wearn, J. T.: *J. Exper. Med.* 56: 919, 1932.
18. Leary, T., and Wearn, J. T.: *AM. HEART J.* 5: 412, 1930.

THE ARTERIAL BLOOD VASCULAR DISTRIBUTION TO THE LEFT AND RIGHT VENTRICLES OF THE HUMAN HEART*

LOUIS GROSS, M.D., AND M. A. KUGEL, M.D.

NEW YORK, N. Y.

IN ORDER to obtain a measure of the actual blood supply to a given mass of myocardium it would be necessary to know, among other things, the exact volume of muscle supplied, the distribution of the capillaries throughout the myocardial mass, the cross-section of the capillary bed (from which the capillary surface area could be determined), the velocity of blood flow through the capillaries and the tension within them. Certainly, no accurate comparison can be made of the nutrition to the two ventricles without a knowledge of the factors mentioned above.

On the other hand, it is not unfair to assume that, other factors being equal, a knowledge of the extent of the capillary bed throws some light on the blood nourishment to a given organ and, therefore, that purely anatomical studies along these lines are not without their interest and value. In the work which we are about to report it should be clearly understood that the term "blood supply" is used in this limited anatomical sense.

It is definitely pertinent to our discussion to mention that the data obtained on this question by the employment of a given technic can never be more accurate than the method itself. Here lies the crux of most of the discussion on the blood supply to the heart, anatomically considered. Up to the present, such studies have been made largely on specimens injected through the coronary arteries. Since it is vital to a critical evaluation of the results obtained from these injected specimens that only the arterial side of the vascular tree be filled, the injection mass used must be of such consistency that it will not pass beyond the capillaries into the venous system. For these purposes either a suspension of gross particulate matter (starch, barium, etc.) or a highly viscous solution (collodion, glue, etc.) is generally employed. These substances never give a complete injection of the capillaries. As a general rule and under the best of conditions one contents oneself with a uniform and even injection of vessels down to the size of arterioles. There can be little doubt that the extent and distribution of these small vessels bear a definite ratio to the ultimate capillary bed. Therefore, in discussing the "blood supply" to the ventricles, the term is limited not only to its anatomical aspects, but

*From the Laboratories of The Mount Sinai Hospital, New York, N. Y. Aided by a grant from the Lucius N. Littauer Fund.

to the information on the capillary bed which can be gleaned from a study of the smaller vessels leading to the capillary distribution. Furthermore, in all probability, the further one follows the arterial tree into its ultimate ramifications, the more closely do these ramifications mirror the entire extent of the capillary bed. We have, therefore, confined our attention to this aspect of the problem.

In choosing the method of injection which is likely to give us the most accurate results, the following factors must be borne in mind:

1. The mechanical factors entering into the injection (temperature, pressure, viscosity, humidity) must be standardized and easily reproducible. This is most important. Variations in technic from specimen to specimen are bound to produce technical artefacts, making comparisons of little value.

2. The mechanical factors must not be such as grossly to distort the organ. Thus, injections with metals or other materials requiring relatively high temperatures tend to shrink the tissues by their cauterizing effect. Injection of highly viscous substances such as collodion, requires very high pressure and a long period of injection, both of which factors are inimical to obtaining an accurate picture of the delicate vascular tree.

3. The injection must be completed in a relatively short time so that the specimen may be fixed and rendered fit for microscopic examination. This examination is most important in order to rule out pathological changes such as, for example, hypertrophy, which are accompanied by corresponding changes in the vascular bed.

4. If the mass is injected through the arterial system (coronary arteries), it should not penetrate into the venous channels. As mentioned before, this is necessary in order not to confuse the arterial and venous beds.

5. The preparation should neither be fragile nor permit of appreciable distortion.

In reviewing the numerous injection methods available it seemed to us that the one least open to criticism was that employed by Gross.^{1, 2} This consists of the injection of a standardized barium sulphate gelatin suspension through the coronary arteries of hearts in which rigor is allowed to pass off. The injection is carried out in a special apparatus which permits of accurate control and standardization of all the mechanical factors. Furthermore, the injection takes approximately one-half hour to complete so that the organ can be fixed at once and rendered suitable for dissection, roentgenological examination, clearing, histological study, etc.

Employing this method in 100 hearts, Gross pointed out in 1921 that the blood supply to the two ventricles was equal at birth and that from then on the left side became relatively richer in its vascular bed as compared to the right. In attempting to arrive at an explanation

for this phenomenon, there was quoted the table of weights of human ventricles compiled by Müller³ on a material of 1,481 hearts. Since there has been some question by Whitten⁴ as to the interpretation of this table, a chart made from it is again reproduced in this report (Chart 1). This chart represents the growth in weight of the left and right ventricles computed from the mean weights of the isolated ventricles in males and females. A glance at this chart shows quite definitely the sharp increase in left ventricular preponderance up to the fourth decade and gradual but slower increase thereafter.

In examining the stereoscopic roentgenograms and cleared specimens it seemed to Gross that this preponderance of left ventricular

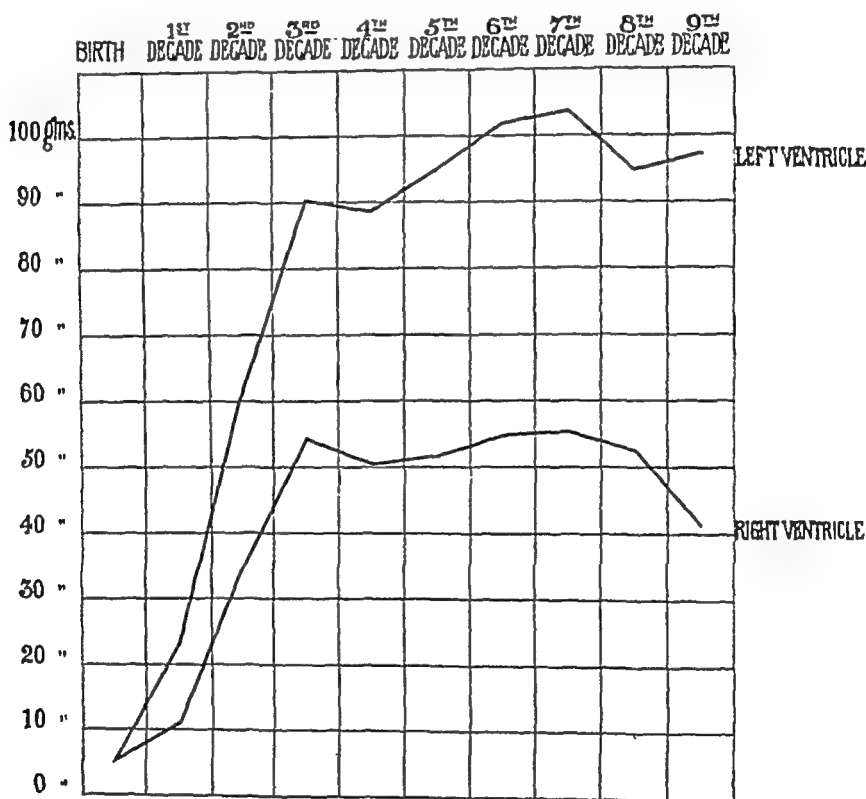


Chart 1.—Graph showing the absolute increasing weight of the right and left ventricles as age advances, and also the relative increasing preponderance of left over right side.

vascular bed over right was even greater than could be accounted for by the change in the proportion of the myocardial masses. He suggested that the right ventricle apparently lagged behind the left in the evolution of its vascular tree.

A complete confirmation of these findings soon followed in the detailed report by Campbell.⁵ In 1930, however, reports appeared by Whitten^{4, 6} in which, by the use of a collodion-corrosion injection technique, conclusions were arrived at which were in some respects in sharp contradiction to those of Gross. Without stating the number of hearts

*Seven are quoted of which two were from fetuses.

examined by his method* (a most important factor in the evaluation of statistical material) Whitten claimed that while the blood supply to the right ventricle was at birth at least as great as that to the left, it soon fell behind the latter in development. A gradual increasing vascular preponderance occurred on the left side which, however, reached its maximum at about the tenth year. From then on no changes took place.

A more serious objection to Gross' conclusions has been raised recently by Ehrich, de la Chapelle and Cohn.⁷ These investigators pointed out the difficulties in interpreting the extent of the injected vascular beds when the heart as a whole is examined roentgenographically, since, as they stated, "it was difficult to estimate and to allow for the increase in density of the left ventricle. The difference is obvious enough when the anterior and posterior walls alone are concerned, but becomes greater in the case of the two lateral walls, through which the rays pass in a direction roughly parallel to an anteroposterior tangent. Clearly, the greater the volume of muscle through which the rays pass, the greater will be the number of vessels photographed. The appearance of relative changes in one ventricle—the right, for example—may, quite aside from the facts, depend upon matters of technical procedure." This objection is valid only to the extent that accurate and fine quantitative comparisons cannot be made by this method. Stereoscopic pictures such as employed by Gross, however, permit of sufficient comparison to determine coarse changes such as he described.

In an attempt to obtain more accurate data, Ehrich, de la Chapelle and Cohn injected fifty-one hearts (forty-one of which were normal) by the method described by Gross. The hearts were fixed in formalin, roentgenographed and cleared. Microscopic sections were taken from the left and right coronary arteries as well as from the left circumflex vessels. These investigators attempted to arrive at an estimate of the distribution of blood to the two ventricles by comparing the number and diameters of the "small branches" on the surface of the cleared hearts. "Small branches" according to them included "all branches larger than a certain size." More precisely, the term referred to all branches of the rami which are macroscopically "just visible." In order to arrive at the total diameter, the authors assumed that all the "just visible" vessels on the surface of the two ventricles must be of the same size. The question as to the accuracy of this and other assumptions made by them will be discussed further.

Dividing thirty-five of their fifty-one hearts into nine groups, these authors observed that the "small branches" increase continuously from birth to the seventh decade, the increase in the left ventricle during this period being 100 per cent and that in the right ventricle 50 per cent. Calculating this increase in terms of per unit mass, however,

they arrived at the conclusion that the developing vasculature was proportionate to the growth of the two ventricles and that there was accordingly no developing relative right-sided anemia as indicated by Gross.

With the above mentioned criticisms in mind, we decided to re-investigate the question by a method which would eliminate, as far as possible, the objectionable features discussed by Ehrlich, de la Chapelle and Cohn. For the reasons already given, it was decided to inject one hundred hearts by the method of Gross. A special effort was made to select specimens which could safely be considered normal. If the clinical history, gross inspection or microscopic examination of the heart indicated a pathological condition, past or present, it was at once discarded.

The essential modification introduced into these studies was to slice the hearts transversely into strips of equal thickness so that a direct comparison could be made of the vasculature within the left and right ventricles, thus comparing unit areas of equal thickness.*



Fig. 1.—Transverse section through the ventricles of an eleven-day-old male infant. (Photograph of roentgenogram from injected specimen.)

TECHNIC

Immediately after injection, the hearts were fixed in 10 per cent neutral formalin saline.† After fixation the hearts were cut into transverse slices, 7 mm. in thickness. This was accomplished by means of a specially devised apparatus which consists of a modified meat slicer. Roentgenograms were taken of the slices according to the following technic: the exposure was three seconds at 30 inches distance, using 88 killivolts peak and 10 milliamperes. The slices were subsequently cleared by the method described by Gross, and sections were taken for histological examination. Large transverse sections, 150 mu in thickness were also cut from a number of hearts by the Christeller frozen section method. For purposes of comparison it will suffice to consider the transverse slices cut approximately one-third of the way down from the auriculoventricular sulcus to the apex. The other sections gave results similar to those to be described.

EXPERIMENTAL

Fig. 1‡ represents the roentgenogram of such a section cut from the heart of an eleven-day-old infant. The arterial vascular preponderance in the right ventricle

*Previous attempts by Gross and Antopol to estimate the ratio of injection mass per gram of myocardium by quantitatively recovering the barium sulphate used in the injection showed a large error due to ultrafiltration effect.

†Solution of formaldehyde, U. S. P., 10 parts; 1 per cent sodium chloride solution, 90 parts. This solution is rendered neutral with a weak alkali.

‡In these photographs of roentgenograms the left ventricle is to the left, the right ventricle to the right and the top of the illustration is the anterior surface of the heart.

is quite obvious. It is interesting to note, too, that even at this early age period the part of the septum which belongs to the right ventricle receives larger blood vessels and more of them than does the corresponding part of the left ventricle.

Fig. 2 is a cross-section from the heart of a three-week-old infant. Here again the right ventricular arterial vascular preponderance is very definite. Not only are the vessels more numerous in the right ventricle and in the right ventricular portion of the septum but their lumina are distinctly larger. It is to be noted that the type of vascular distribution is the same in both ventricles, namely, the superficial



Fig. 2.



Fig. 3.

Fig. 2.—Transverse section through the ventricles of a three-week-old male infant. (Photograph of roentgenogram from injected specimen.)

Fig. 3.—Transverse section through the ventricles of a five-month-old male infant. (Photograph of roentgenogram from injected specimen.)

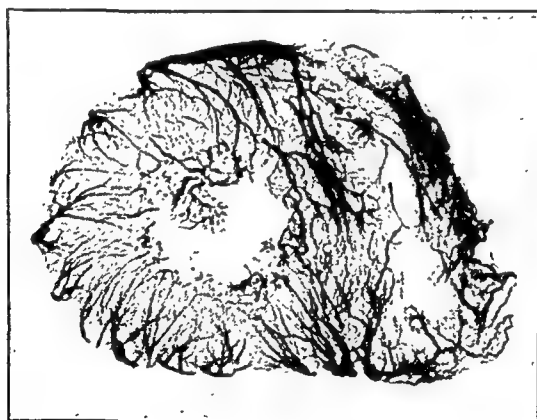


Fig. 4.—Transverse section through the ventricles of a four-year-old male child. (Photograph of roentgenogram from injected specimen.)

vessels rapidly dichotomize and form a series of broomlike structures which penetrate through the ventricular wall at right angles to the surface, reaching almost to the endocardium.

At the fifth month of life (Fig. 3) the myocardial preponderance of the left ventricle over the right is definitely established. Nevertheless, it will be noticed that for a given area of myocardium the amount of fair-sized and fine vessels is approximately the same in both right and left ventricles.

The same statement may be made of the four-year-old infant's heart represented in Fig. 4. Particular attention should be paid to the fact that both the left and right ventricular portions of the interventricular septum are equally richly supplied with fine blood vessels.

The same description also holds true for the nine-year-old heart pictured in Fig. 5. Here the broomlike arrangement of the myocardial trees is beautifully represented. Since the right ventricle is conspicuously thinner than the left, it will be observed that the myocardial vascular brooms take on a slanting arrangement in the former. Whitten has called attention to this and believes that it has some significance in reference to the lesser frequency of arteriosclerosis in the right cor-

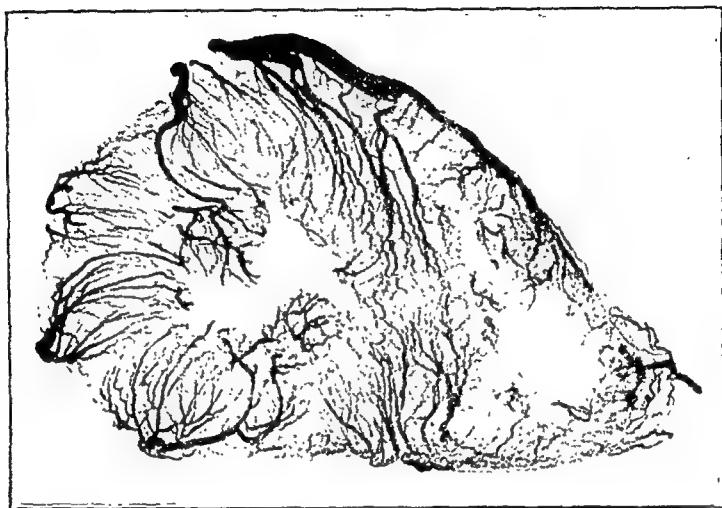


Fig. 5.—Transverse section through the ventricles of a nine-year-old male child (Photograph of roentgenogram from injected specimen)

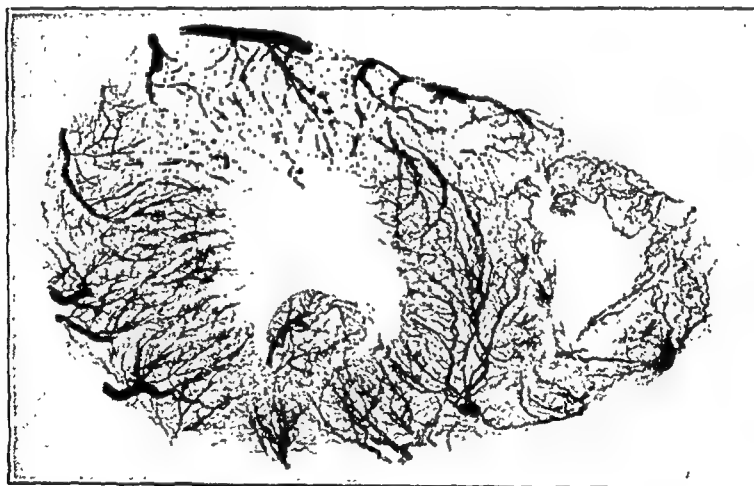


Fig. 6.—Transverse section through the ventricles of an eighteen-year-old male. (Photograph of roentgenogram from injected specimen)

onary branches as compared to those of the left. This question will be discussed subsequently. At this age period the proportion of small and large blood vessels to left and right ventricles is still approximately equal.

In Fig. 6, a cross-section of the myocardium of an eighteen-year-old boy, several differences are becoming discernible. By close inspection it can already be observed that, per unit area of myocardium, the left ventricle is somewhat richer in blood vessels. This is particularly well brought out in the interventricular septum. Another important factor which can be noted is that the septal anastomoses are becoming somewhat more conspicuous (better seen on stereoscopic examination).

By the age of twenty-nine years (Fig. 7) it becomes quite clear that the left ventricular myocardium is richer in blood supply than the right. Inspection of the myocardium of the two ventricles and particularly of the septum shows this quite distinctly.

Fig. 8 (heart of thirty-seven-year-old patient) shows very beautifully the intensely rich blood supply of the left ventricle and the definitely lesser blood supply of the right ventricle. The fact that we are here examining similar thicknesses of

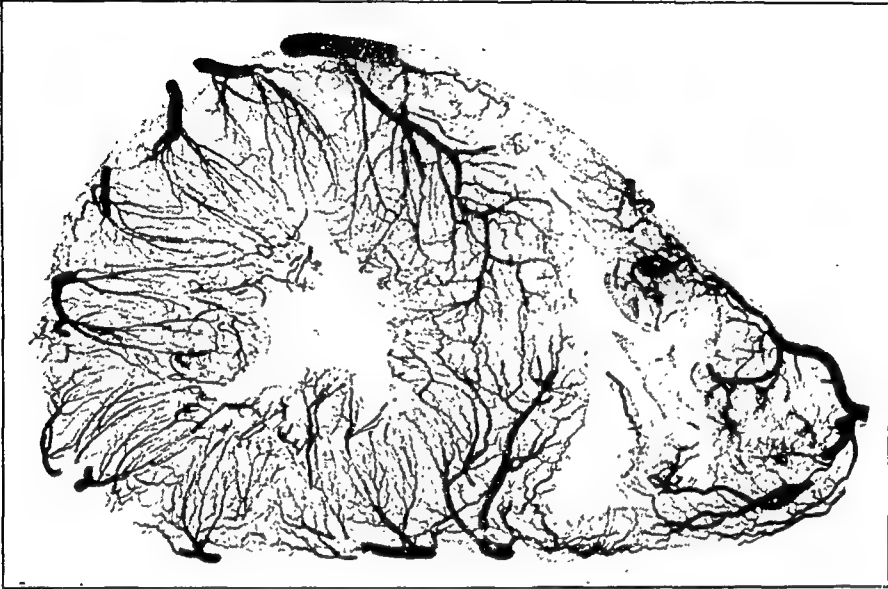


Fig. 7.—Transverse section through the ventricles of a twenty-nine-year-old male. (Photograph of roentgenogram from injected specimen.)

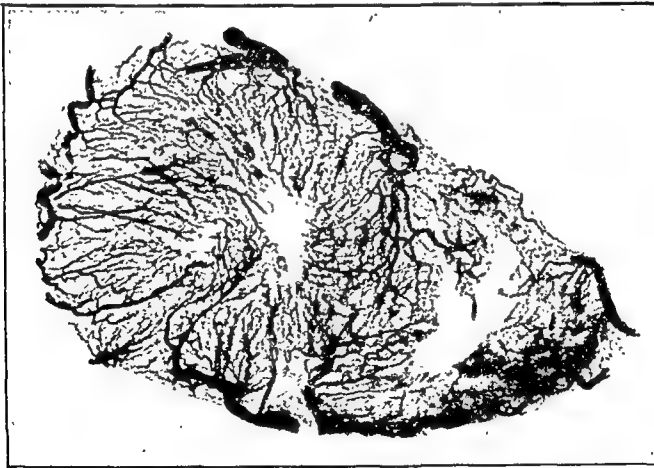


Fig. 8.—Transverse section through the ventricles of a thirty-seven-year-old female. (Photograph of roentgenogram from injected specimen.)

specimens may bear repetition. Note the distinctly richer blood supply of the left ventricular portion of the septum as compared to the right and the very markedly increased septal anastomotic vessels. This well-established left ventricular arterial preponderance is now carried on consistently.

Fig. 9, which represents the heart of a forty-three-year-old person, shows the rich left ventricular supply, the exceedingly rich blood supply to the papillary muscles of the left ventricle, the considerably lesser distribution of vessels in the right

ventricle and in the right ventricular septum. The septal anastomoses are very distinct. It is to be noted in this illustration that because of the slightly greater thickness of the right ventricle, the broomlike structure of the arterial dichotomy reappears.

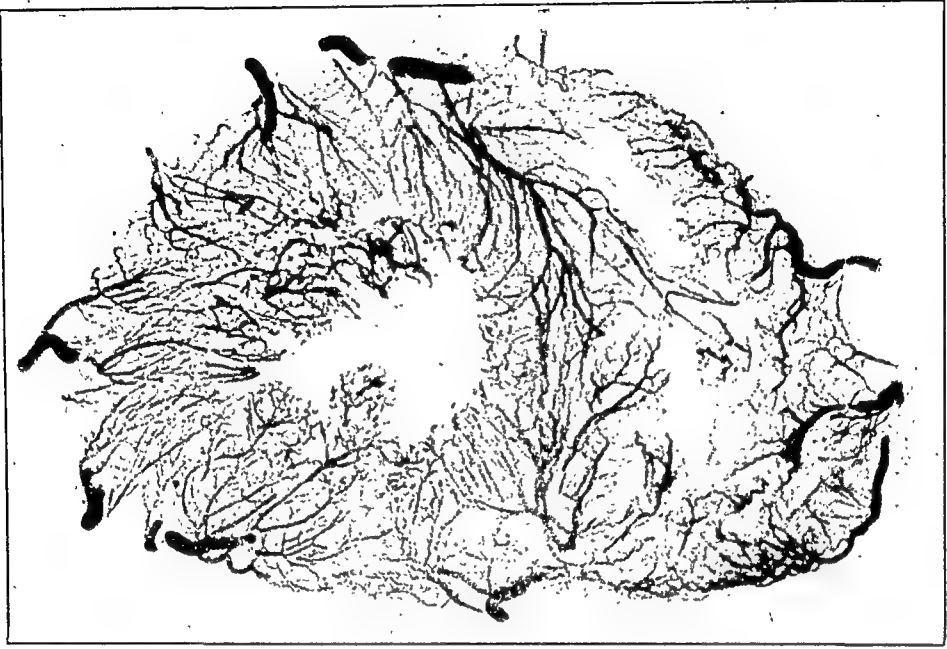


Fig. 9.—Transverse section through the ventricles of a forty-three-year-old male. (Photograph of roentgenogram from injected specimen.)

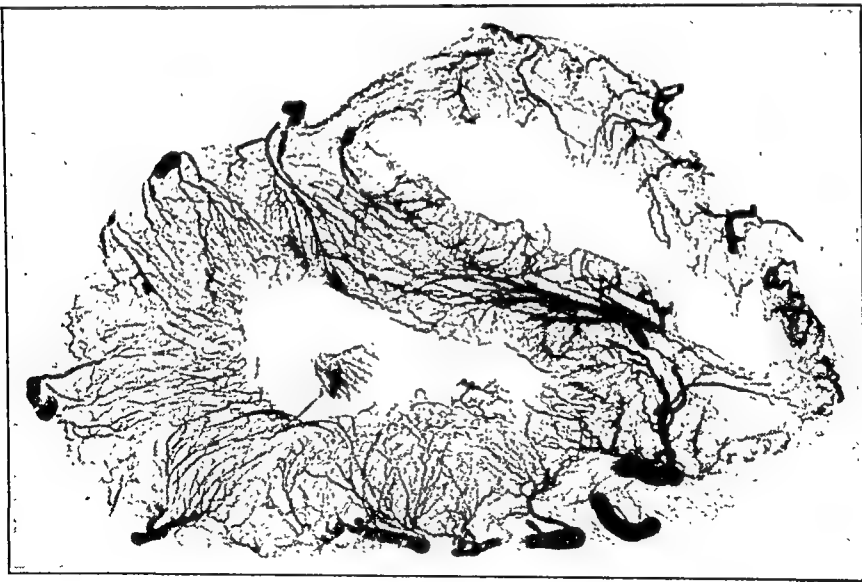


Fig. 10.—Transverse section through the ventricles of a forty-five-year-old male. (Photograph of roentgenogram from injected specimen.)

Fig. 10 (patient forty-five years old) again shows the definite left ventricular arterial preponderance and the consistently richer septal anastomoses. Here the right ventricular wall is somewhat thinner with some loss in the regularity of the broomlike arterial dichotomy.

Increasing age periods now show as the most conspicuous changes an even wider and richer septal anastomosis with persisting and increasing left ventricular vascular preponderance. This is seen in Fig. 11, which represents a cross-section of the heart of a sixty-year-old person.

Fig. 12 is a cross-section of the heart (patient thirty-two years old) taken from a specimen which shows an unusually beautiful injection. This was probably due



Fig. 11.—Transverse section through the ventricles of a sixty-year-old female. (Photograph of roentgenogram from injected specimen.)

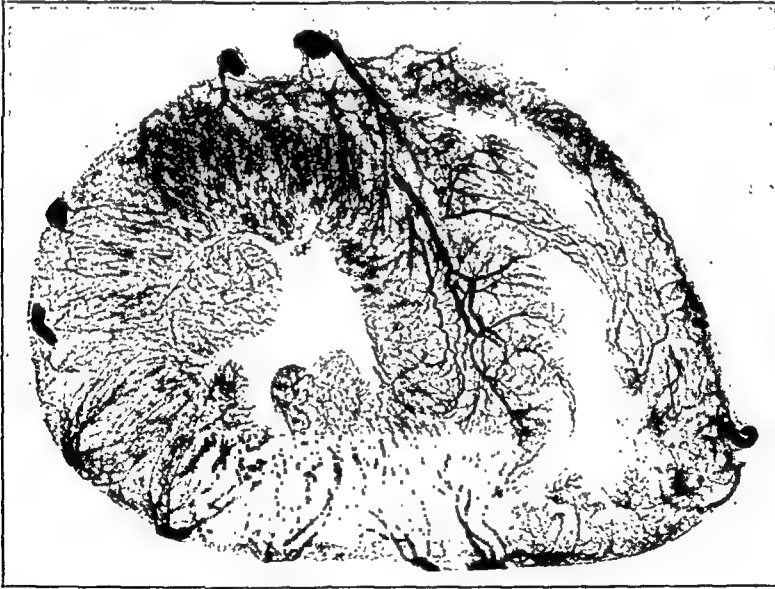


Fig. 12.—Transverse section through the ventricles of a thirty-two-year-old male. (Photograph of roentgenogram from injected specimen.)

to the fact that the heart was injected for a somewhat longer period of time and was completely flaccid before the injection. The striking difference in vascularity as between the left ventricle and the right leaves no question whatsoever with regard to the left ventricular vascular preponderance at this age period. One could not, of course, count these vessels since they are so numerous, but a simple inspection is quite sufficient to make this point clear. In particular, there is to be noted the amazing difference between the fine vascular distribution in the left ventricular

septum as compared with that of the right. Because of the excellence of the injection of this specimen, Christeller frozen sections were studied under the binocular microscope. It was at once evident that it would be highly inaccurate to attempt to count the finest vessels in the myocardium. Here, however, a simple examination again amply confirmed the observations made by the examination of roentgenograms and cleared specimens.

Although only twelve illustrations are submitted in this article, it may be stated at once that in our observation of the hundred cases which form the material of this paper, the rather abrupt shifting of vascular preponderance from the right side to a state of where both sides are about equally supplied, occurred relatively early in life (within the first few months). Then came a period of approximately one decade when it was somewhat difficult to decide which side of the heart contained more blood vessels per unit volume. From the first decade on, however, the increase in left ventricular vascular preponderance was consistent and gradual, and with it came the widening of the septal anastomotic channels (better seen in stereoscopic examination and in the cleared specimens).

A study of all the preparations leaves two very definite impressions in mind: the eventual development of left ventricular vascular preponderance and the increase in septal anastomoses seen particularly well after the third decade and increasing consistently with age.

DISCUSSION

A discussion of the above mentioned findings must concern itself largely with the reasons for the discrepancies between our conclusions and those of Whitten and of Ehrich, de la Chapelle and Cohn. With regard to Whitten, it may be said that undoubtedly the paucity of his material together with the unusually unsuitable technic employed by him may have been responsible. It is to be remembered that the technic used by Whitten (collodion-corrosion method) requires several days for completion, does not render the heart suitable for microscopic examination, requires enormously high pressures which may possibly distort the preparation and has a tendency to leak from the arterial to the venous side. A brief reference to our earlier discussion on the criteria of adequate injection technic will show at once that Whitten's technic leaves much to be desired.

It has already been mentioned that Whitten questioned Gross' conclusions that Müller's tables of weights furnished evidence of a consistently increasing left ventricular myocardial preponderance from birth to the ninth decade. In substantiation of his contention Whitten also quoted a table of weights from Müller's monograph. The difference here is obviously due to the fact that Whitten's criticism is based on a table presenting entirely different data; indeed, data which include the very questionable and arbitrary division of the septum into its proportions as to the left and right ventricles. The table quoted by Gross deals only with the isolated ventricles exclusive of the septal portions.

The discrepancy in the findings of Ehrich, de la Chapelle and Cohn can be accounted for in several ways. First, these authors assume

that a "small branch" (superficial) conveys the actual supply to what may be regarded as a unit territory. In calculating their results, however, they also tacitly assume that "unit territory" is equivalent to unit mass of myocardium. This is exactly where the difference lies as between their conclusions and our observed results. The territory supplied by a "small branch" in the left ventricle is considerably smaller than that supplied by a "small branch" in right ventricle as our illustrations clearly show. These authors find that the number of "small branches of the left ventricle (superficial) increases during the period of life about twice as much as the right one." Since, however, the left ventricle during this period enlarged about twice as much as the right, they conclude that the blood supply of the two ventricles increases with increasing years in direct proportion to weight. However, when these authors use the term "small branches of the left ventricle," they really refer to "small branches *on the surface of* the left ventricle." Obviously, the very increase in thickness of the left ventricle carries with it at least a proportionate increase in "small branches of the ventricle." This has not been taken into account by Ehrlich, de la Chapelle and Cohn. Furthermore, their counts were made on thirty-five hearts, a number in our opinion too few for such detailed analysis. An attempt made by us to count these superficial vessels was rather unsuccessful. We found it extraordinarily difficult to determine what vessels should be considered as "just visible" and what not. An examination of their own Curve 2 (p. 263 of their article)⁷ discloses not inconsiderable variations in their figures. Moreover, the correctness of the assumption by these authors that the diameters of the counted "small vessels" on the surface of both ventricles are the same has by no means been substantiated. On the whole it seems to us that the method used by them is subject to far more inaccuracies than even the first method used by Gross, viz., direct inspection of the stereoscopic roentgenograms.

We do not wish to enter into a discussion at this time of the possible physiological significance of this gradually developing left ventricular vascular preponderance. Experiments are under way to investigate this point. The importance of the gradually developing septal anastomoses with age has already been emphasized by Gross, who suggested that this may serve as a compensatory factor during the later age periods when sclerotic changes begin to appear particularly in the branches of the left coronary artery. Histological examination of the age period changes in the coronary arteries to be published shortly by Gross, Kugel and Epstein shows that with advancing life there is a gradual fibro-elastification of the smaller myocardial vessels, particularly in the left ventricle, with some disappearance of smooth muscle elements. These vessels are consequently rendered relatively passive to vasomotor impulses. Whether the septal anastomotic in-

crease is a compensatory process as a response to these regressive changes in the left ventricular myocardial blood vessels can only be surmised. In a later publication, it will be shown that these septal anastomotic vessels play an extraordinarily important rôle in coronary artery disease in which myocardial infarction takes place.

CONCLUSION

By means of a new technic whereby it is possible to study the vascular distribution in the myocardium and to compare unit areas in the left and right ventricle, it has been definitely demonstrated that early in life there is a right ventricular vascular predominance, that there soon follows an equalization of the vascular supply which lasts for approximately one decade and that thereafter the left ventricular myocardium assumes an increasing preponderance in its vascular bed over that of the right.

It has also been shown that, particularly after the third decade in life, the septal anastomoses increase very conspicuously in their extent.

Both of these observations confirm the earlier report by Gross in this field.

An explanation is suggested for the reported differences from these conclusions.

REFERENCES

1. Gross, Louis: *The Blood Supply to the Heart*, New York, 1921, Paul B. Hoeber.
2. Idem: A New and Improved Injection Apparatus, *J. Lab. & Clin. Med.* 13: 257, 1927.
3. Müller, W.: *Die Massenverhältnisse des menschlichen Herzen*, Hamburg und Leipzig, 1883, Leopold Voss.
4. Whitten, Merritt B.: A Comparison of the Blood Supply of the Right and Left Ventricles in Childhood, *Arch. Int. Med.* 45: 46, 1930.
5. Campbell, J. S.: Stereoscopic Radiography of the Coronary Circulation, *Lancet* 2: 168, 1928.
6. Whitten, Merritt B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, *Arch. Int. Med.* 45: 383, 1930.
7. Ehrlich, Wilhelm, de la Chapelle, Clarence, and Cohn, Alfred E.: *Animal Ontogeny. B. Man. I. A Study of the Coronary Arteries*, *Am. J. Anat.* 49: 241 1931.

CARDIAC HYPERTROPHY OF UNKNOWN ETIOLOGY IN YOUNG ADULTS

A CLINICAL AND PATHOLOGICAL STUDY OF THREE CASES*

ROBERT L. LEVY, M.D., AND LOUIS M. ROUSSELOT, M.D.
NEW YORK, N. Y.

IN THE course of two and a half years, there have been observed three young men who presented an unfamiliar picture. Clinically, the outstanding feature was a considerable degree of cardiac enlargement, for which no cause was apparent. All died within a year after the symptoms became well established. The lesions in the three hearts, as studied at autopsy, though exhibiting many points of similarity, were not identical. The etiology remained obscure.

CASE REPORTS

CASE 1.—Unit No. 69800. S. R., white male, aged twenty-nine years, automobile mechanic, married, was first admitted to the hospital on September 17, complaining of palpitation which had been present continuously for two and one-half months. His father died at the age of fifty-six, of heart disease. He had been unusually healthy. Tonsillectomy was performed at the age of eleven. He had gonorrhea at twenty, but denied syphilis. At the age of twenty-four, he was in South America for a short period, while in the Navy. He had been married for six years. His wife and two children were living and healthy; there had been no miscarriages. His consumption of alcohol and tobacco was very moderate. For twelve years, he had been an automobile mechanic. His usual weight ranged from 190 to 210 pounds.

He first was conscious of irregularity of the heart five years previously while working in South America. After a day's labor, during which he was much exposed to sun and fumes, he would lie down to rest. It was then that he became aware of the irregular and rapid beating of his heart, which occurred in paroxysms lasting from five to fifteen minutes. The attacks increased in frequency until he had several each day. After his return to New York they became less frequent, recurring at irregular intervals. For two and one-half months, however, tachycardia had persisted almost continuously and he had felt weak. He consulted several physicians without relief. He was unable to obtain the proper amount of sleep because of the pounding of his heart and throbbing of his arteries.

Examination showed a large, well-developed man, who appeared to be quite ill. There was no dyspnea or cyanosis. The tonsils had been well removed. The thyroid was not palpable. The lungs were clear. The heart was considerably enlarged, dullness extending 13 cm. to the left in the fifth space, and 4 cm. to the right in the fourth space. The rate was variable, at times 120 to 160, with regular rhythm, then a few irregular beats, followed by a sudden drop to 60. The sounds

*From the Medical Clinic of the Presbyterian Hospital, and the Departments of Medicine and Pathology of the College of Physicians and Surgeons, Columbia University.

Read before the Association of American Physicians, Washington, D. C., May 9, 1933.

were of moderate intensity. There was splitting of the first sound at the apex. No murmurs were heard. The peripheral vessels were not thickened. The blood pressure was 110/80 mm. The liver was not enlarged. There was no clubbing of the fingers. No edema was present.

The temperature was normal and remained so throughout his stay in the hospital. The blood count showed: R.B.C. 6,000,000; hemoglobin (Dare) 95 per cent; leucocytes 12,000, with 63 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The urine contained a very faint trace of albumin, but no casts or red blood cells. X-ray films of the teeth did not show any root abscesses.

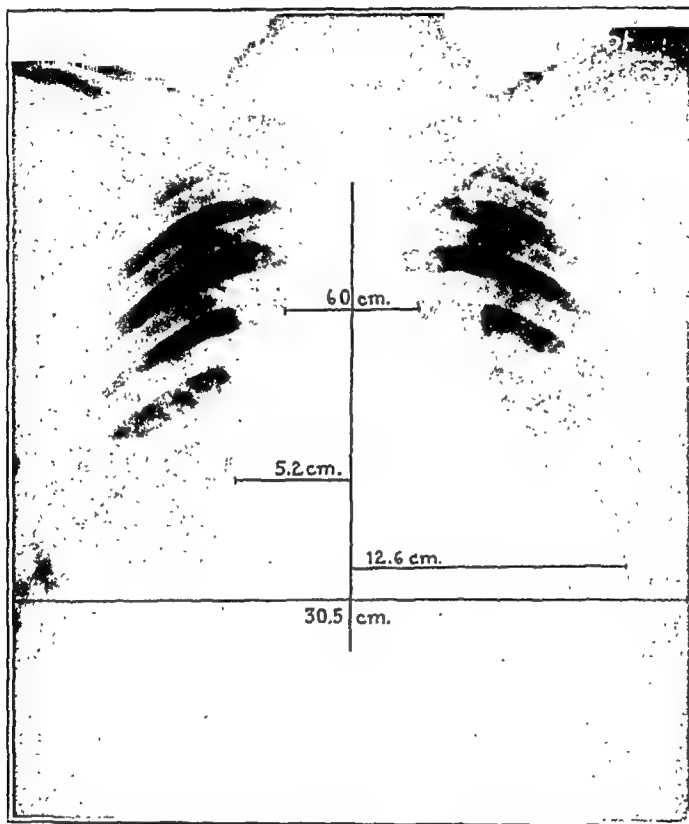


Fig. 1.—(Case 1) Teleroentgenogram of the heart, taken four days after the patient's first admission to the hospital. The enlargement is chiefly to the left.

A teleroentgenogram of the heart showed the transverse diameter to be increased, but the aorta was not widened. The total transverse diameter measured 17.8 cm., the great vessels 6.0 cm., and the internal diameter of the chest 30.5 cm. (Fig. 1).

The heart rate varied greatly from day to day and from hour to hour. Electrocardiograms were made daily and often, several times in the course of twenty-four hours. The dominant rhythm was a tachycardia having its origin in the junctional tissues, with rate of 50 to 160. Numerous ventricular premature beats, arising both in right and left ventricles, occurred. On a number of occasions transitions were photographed, showing changes in rate and in the origin of the pacemaker (Fig. 2, A). The P-R interval, when it could be measured, varied from 0.22 to 0.31 second, and there was widening of QRS when nodal rhythm, with slow rate, was present. The T-wave was at first inverted in Lead I and upright in Leads II and III, but later, following administration of digitalis, T₁ and T₂ also became inverted.

Administration of quinidine, by mouth, in moderately large doses, did not affect either the rate or the rhythm. The use of digitalis, first in full doses, and then in maintenance ration, slowed the rate to 60, with occasional short paroxysms of tachycardia to 120. The blood pressure rose to 130/70. On discharge, after four weeks in the hospital, the patient felt greatly improved, and was instructed to continue with small daily doses of digitalis.

He did not return to the out-patient department for further observation and was lost sight of until June 4 of the following year (eight months later), when he came

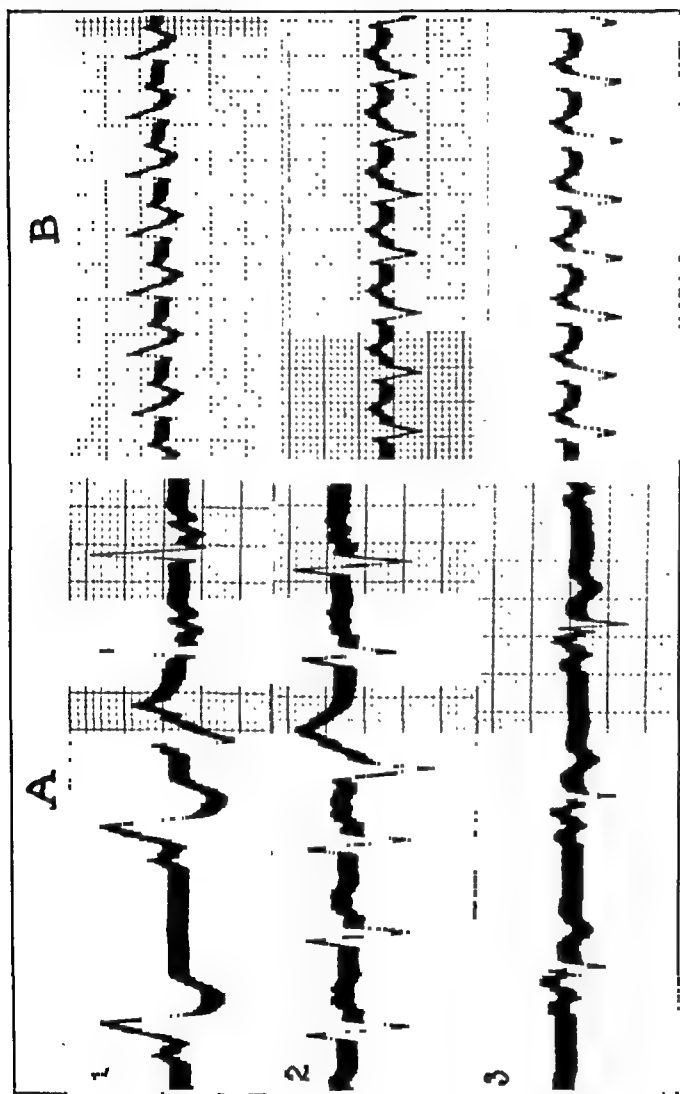


Fig. 2.—(Case 1) A. September 21, four days after the first admission to the hospital. In Lead I is shown the transition from a rhythm initiated in the upper portion of the functional tissues, with rate of 50 and aberrant ventricular complexes, to one originating lower in the A-V bundle, with rate of 120 and normal intraventricular conduction time. The shift in the location of the pacemaker is ushered in by a premature beat arising in the ventricle. In Lead II, A-V nodal rhythm continues, as at the end of Lead I. In Lead III, the impulse again has its origin in the upper part of the node, the rate being 64. The QRS interval is again widened.
B. June 7 of the following year (three days before death). Auricular tachycardia; rate 170. P-R (conduction) time is 0.19 second. There has been a marked change in the form of the complexes.

to the clinic desperately ill. He stated that after leaving the hospital he again went to South America on a job, but had to leave after five weeks, because of recurrence of the paroxysms of tachycardia. He returned to this country two weeks ago, and since that time had great difficulty in getting his breath. He had taken digitalis in liquid form, without benefit.

On admission, he was cold and a clammy sweat covered the skin. The respirations were rapid and shallow. The pulse was barely palpable. The heart rate was about 180, and the rhythm apparently regular. The temperature was 99.4° F. The blood pressure was 134/90. The blood Wassermann reaction was again nega-

tive. A blood culture showed no growth. The leucocyte count was 13,000, with 42 per cent polymorphonuclears. There was no anemia. The blood urea was 41 mg. per 100 c.c. Electrocardiograms showed at times auricular tachycardia, with rate of 170 and incomplete bundle-branch block; and at other times A-V nodal rhythm with rate of 70 to 80, with complete bundle-branch block, and numerous ventricular premature beats. When the rate was slow, QRS measured 0.17 second, R was notched and T was inverted in all leads. The records were very different in form from those previously obtained. (Fig. 2, B.)

Dyspnea persisted and was more marked during the paroxysms of tachycardia. Administration of large doses of digitalis was without apparent benefit. He began spitting up blood, evidently as a result of pulmonary infarction. The temperature rose to 103.4° F., and the leucocyte count to 31,000, with 79 per cent polymorphonuclears. Orthopnea and prostration became extreme, and he died on June 10, six days after entering the hospital.

Autopsy No. 10017.—The autopsy was performed by Dr. L. M. Rousselot. External examination showed slight cyanosis of the face and nail-beds. There was pitting edema of the crural regions and feet.

Thoracic Cavity: The pericardial sac contained 30 c.c. of clear, straw-colored fluid. *In situ*, the heart appeared to be enormously enlarged, measuring 19 cm. in its maximum transverse diameter. The right pleural cavity contained 100 c.c. of thin, blood-tinged fluid.

Heart: The heart weighed 740 grams. There were numerous pericardial hemorrhages. A few epicardial hemorrhages were seen on the posterior surface of the right auricle, and also on its lateral surface near the base of the superior vena cava. The right auricle was covered with numerous fine, fibrous tabs. A small tendinous plaque, measuring 1 cm. in diameter, was found near the base and posterior surface of the right ventricle. All the chambers of the heart were greatly dilated. The musculi pectinati of the right auricular appendage were hypertrophied; no thrombi were present. The leaflets of the tricuspid valve were enlarged, but the cusps were not thickened and the chordae tendineae were thin and delicate. The columnae carnae and papillary muscles in the right ventricle were markedly hypertrophied. There was no scarring of the wall on the right side. The pulmonary leaflets did not present the same relative increase in size as did those of the tricuspid valve. The wall of the left auricle was moderately hypertrophied. The mitral cusps were enlarged and thickened. There was edema of the free margins, and near the line of closure of the aortic leaflet there were a number of fine granular excrescences, covering an area 0.5 cm. in diameter. A small area of atheroma was found at the base of this same leaflet. The papillary muscles, columnae carnae, and myocardial wall of the left ventricle were hypertrophied. The chordae were thin and delicate. There was gross scarring of the posterior papillary muscles of the aortic leaflet of the mitral valve. The cavity of the left ventricle, in addition to being dilated, extended well down to the apex, and here the wall of the myocardium was quite thin, measuring 0.5 cm. This was in contrast to the remainder of the wall of the ventricle, which measured 2.4 cm. in thickness. Several small thrombi filled in the recesses between the columnae carnae. Beneath the aortic ring, there was slight thickening of the septal surface of the endocardium, which at this place measured 2 mm. The aortic leaflets were increased in size, but not thickened.

The coronary arteries were not occluded at any point. In the anterior descending branch there were many fine areas of atherosclerosis without calcification.

There were multiple infarcts in the lungs, and a single infarct was present in the right kidney. There was chronic passive congestion of the lungs, liver, spleen, pancreas, and kidneys.

Microscopic Examination of the Heart.—Myocardium: A majority of the muscle fibers were hypertrophied; their striations were distinct and the nuclei were well defined. In the areas of infarction, there appeared varying stages of degeneration and repair. In places, the muscle fibers had lost their characteristic, intense staining reaction, and occasionally showed vacuolated cytoplasm, with pyknotic nuclei. Other areas of the myocardium were replaced by diffuse connective tissue scars.

Endocardium (interventricular septum): A dense layer of fibrous tissue was seen beneath the endothelium. This was infiltrated with small and large lymphocytes. In places, the endothelium was denuded, and attached to these sites were small thrombi.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; infarcts of the heart, old and recent; fibrous thickening of the endocardium of the left ventricle; thrombi in the left ventricle; infarcts of the lungs; infarct of the right kidney; right hydrothorax; edema of the lower extremities; chronic passive congestion of the lungs, liver, spleen, pancreas, and kidneys; congenital malformation of the aorta (common origin of the innominate and left common carotid arteries); congenital malformation of the lungs (anomalous fissuration).

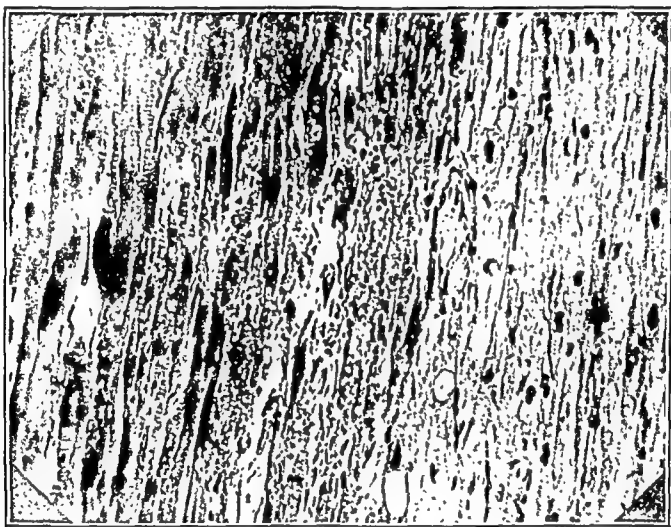


Fig. 3.—(Case 1) Section through the myocardium, showing an area of infarction of recent origin. Hematoxylin and eosin; $\times 160$.

Final Note.—Cardiac hypertrophy and dilatation were the dominant features of the post-mortem examination. There were no inflammatory or degenerative lesions in any part of the cardiovascular system. The various embolic phenomena were secondary to the intracardiac thrombi. After careful study of all of the material, no etiological basis for the heart lesion could be found.

CASE 2.—Unit No. 73296. E. R., a white, single male, aged eighteen years, was a high school student. The patient was admitted to the hospital on August 4, complaining of rapid heart action of eight weeks' duration. The family history was entirely irrelevant. The parents were intelligent, and the young man lived in comfortable surroundings, in a private house. He had enjoyed good health. At the age of eight, he had influenza, and at fourteen, had dry pleurisy. He had had only one attack of tonsillitis, which occurred at the age of fifteen. Two and one-half years before admission (at the age of fifteen and a half years) he had an attack of palpitation, which lasted for two days and stopped after taking digitalis. No other cardiac symptoms followed this short paroxysm, and he had been remarkably well.

He lived the normal life of a high school boy, and worked during the summers. He took no tobacco or alcohol.

Eight weeks before admission to the hospital, he became aware of rapid heart action, which came on suddenly after eating ice cream. Tachycardia persisted for ten days, with rate of about 120, and stopped abruptly after taking digitalis and resting in bed. For four days, the pulse rate remained slow. During this time,

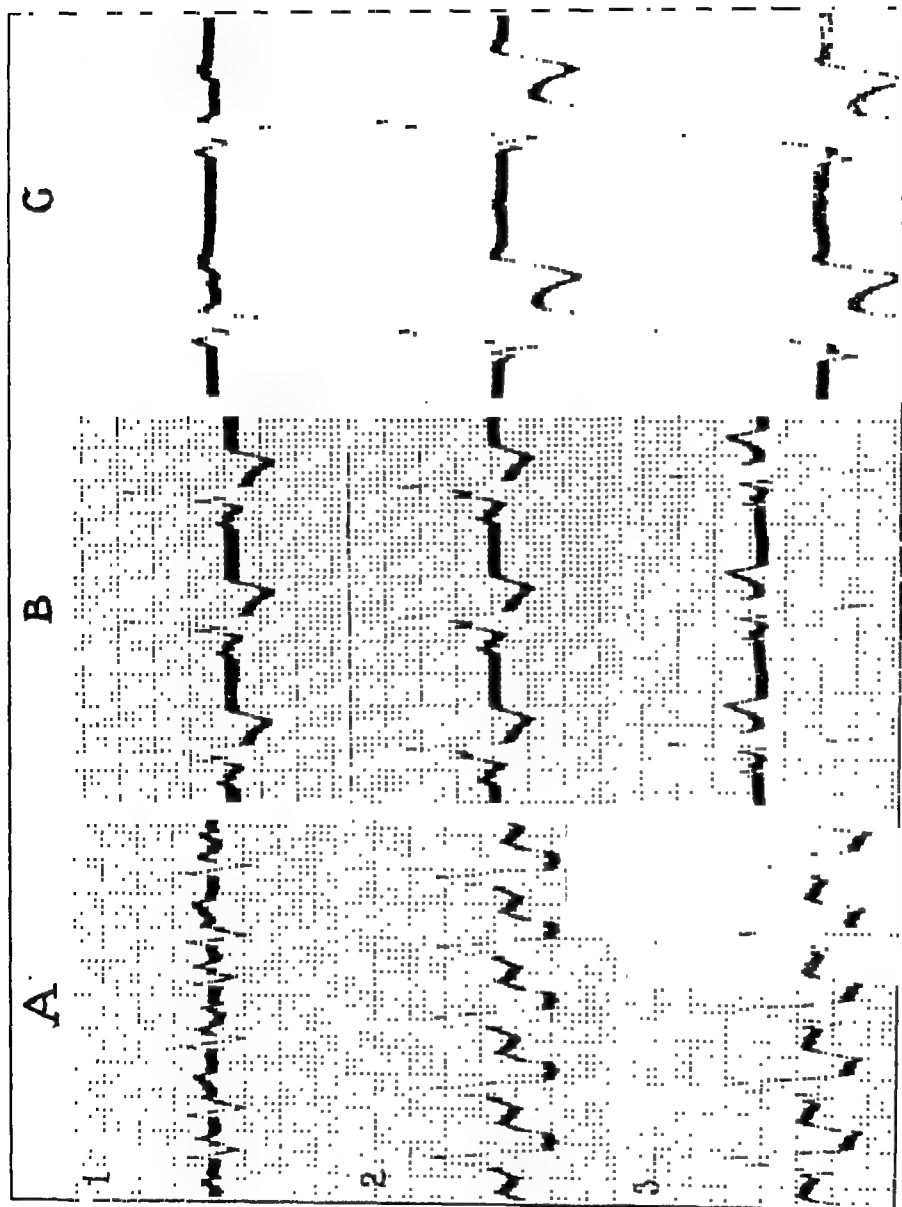


Fig. 4.—(Case 2) A. August 14 (first admission to the hospital). Auricular tachycardia, with rate of 140. In Lead I, occasional premature beats appear, which originate probably in the ventricle. P-R (conduction) time is 0.12 second. There is widening and deformity of the QRS group. B. Sept. 7. Regular sinus rhythm, with rate of 74. The T-wave is inverted in Leads I and II, and there is still disturbance in intraventricular conduction. C. Oct. 2. Junctional (A-V nodal) rhythm, with rate of 52. The pacemaker has shifted and there are striking changes in the form of the complexes. The T-wave is now partly upright in Lead I, but sharply inverted in Leads II and III.

he felt poorly, and vomited once. His physician said that he had heart-block and gave him adrenalin. At the end of this four-day period (six weeks before admission) his pulse again suddenly rose to about 120, while he was lying down after supper, and the rapid rate continued, except for occasional short intervals when his physician pushed digitalis therapy. Because of the previous occurrence of block, this drug had been used with caution. The patient had been in bed for six weeks. There was no precordial pain, dyspnea, or edema.

Examination showed a tall, poorly developed, pale, young man, breathing easily and quite comfortable. The tonsils were small and buried. There were no signs

of thyroid disturbance. The heart was enlarged, dullness extending 13 cm. to the left in the fifth space, and 5 cm. to the right in the fourth space. The rhythm was regular; the rate approximately 120 and regular. The sounds were of good quality and no murmurs were heard. There was no thickening of the peripheral vessels. The blood pressure was 130/80. The temperature was 100.2° F. Blood count showed: R.B.C. 4,070,000; hemoglobin 70 per cent; leucocytes 9,100, with 75 per cent polymorphonuclears. A Wassermann reaction of the blood was negative. The blood culture was negative. The urine showed no albumin or sugar. Under the microscope, no red blood cells were seen.

A teleroentgenogram of the chest showed the heart shadow to be enlarged in all diameters and the auricles were increased in size. There was no dilatation of the aorta. The transverse diameter of the heart measured 17 cm., the aorta 6.5 cm., and the internal diameter of the chest 26 cm.

The first two electrocardiograms showed auricular tachycardia, with rate of 145 to 160. The R-wave was notched and the T-wave inverted in all leads. Subsequent records showed considerable variability in the form of the complexes, with short runs at somewhat faster rate, due to beats originating at other foci in the ventricles or junctional tissues (Fig. 4). Digitalis and quinidine had but little effect on either the rate or rhythm. The temperature, for the most part, was normal, with occasional brief spikes to 100.4° F., or less.

On September 6 (about a month after admission) tonsillectomy was performed under local anesthesia. Microscopic examination of sections of the tonsils showed deep crypts without pus. The capsules were thickened and there was the usual infiltration with lymphocytes which is seen in chronic tonsillitis. On the morning following the operation, sinus rhythm appeared, with rate of 78. Incomplete bundle-branch block was present, with QRS of 0.13 second. The P-R interval was 0.14 second. T₁ was inverted, and T₂ and T₃ were upright. Sinus rhythm persisted for about two weeks, and subsequently A-V nodal rhythm, with bundle-branch block, was observed. T₁ became diphasic, T₂ and T₃ inverted, although no digitalis was given during this time. Salicylates were given in moderate dosage, because it was believed that the condition might be rheumatic in origin. Following operation, the temperature gradually returned to normal. The patient was discharged on October 10 (two months after admission), much improved. He had gained several pounds in weight.

He apparently got on comfortably for three months, but was readmitted on January 11 of the following year, again complaining of tachycardia. The rapid rate began three weeks previously, again following excessive indulgence in ice cream. He was put to bed and given digitalis for two weeks; he then became nauseated and vomited. The tachycardia persisted. He complained of having had several fainting spells in bed, associated with dyspnea and increase in the heart rate.

Examination on admission showed a temperature of 100° F., heart rate of 124, with regular rhythm, and blood pressure 94/70. A systolic murmur was heard at the apex, which had not been observed previously. The spleen was not palpable. The heart size was as noted at the time of the former admission. Examination of the blood showed: R.B.C. 4,560,000; hemoglobin 73 per cent; leucocytes 8,300, with 86 per cent polymorphonuclears. An electrocardiogram showed auricular tachycardia, with rate of 145. The rhythm was quite regular. The ventricular complexes were aberrant, and resembled very much the record made at the time of his first admission to the hospital. On the following evening, the temperature had risen to 101.4° F. The rhythm became irregular and somewhat slower. It was thought that auricular fibrillation was present, although no cardiogram was made. On the third day in the hospital, following an enema and while sitting on the bed-pan he gave a groan and died suddenly within a few seconds.

Autopsy No. 10125.—The autopsy, performed by Dr. W. C. von Glahn, was limited to examination of the heart and lungs. External inspection showed no edema of the feet or legs. There was intense cyanosis of the nail-beds and moderate cyanosis of the lips.

Thoracic Cavity: The pericardial sac contained only about 15 c.c. of blood-tinged fluid. The apex of the heart was against the lateral chest wall in the left midaxillary line. The transverse diameter of the heart, in situ, was 16.5 cm. Over the base of the heart, in the region of the great vessels, were fibrous adhesions.

Heart: The heart was greatly enlarged and weighed 750 grams. The apex was formed about equally by the right and left ventricles. The capillaries in the epicardium were very prominent. On the posterior surface of the left ventricle, about 1.5 cm. below the auriculoventricular groove and covering this groove, was a small, tendinous plaque. A few hemorrhages were found beneath the epicardium of the right auricle. The heart muscle was firm. The right auricle was greatly enlarged; its walls were enormously hypertrophied, measuring 11 mm. in the thickest portion. The endocardium of the auricle was thickened in places to such an extent that it was no longer possible to see the underlying myocardium. The tricuspid valve leaflets were thin and delicate. The papillary muscles and columnae carnae of the right ventricle were enormously hypertrophied, as were also the muscoli pectinati of the auricle. The endocardium of this ventricle was thin and transparent, except for a few small areas near the apex, where it was grey and somewhat opaque. At the apex of the right ventricle were four slightly irregular, greyish masses, surrounded by post-mortem clot and not attached to the wall of the ventricle at any point. The largest of these was not more than 1 cm. in its greatest dimension. They were soft and lay between the hypertrophied columnae carnae. It was impossible to say from the gross appearance whether these were thrombi or represented post-mortem clot. The conus of the ventricle was greatly dilated. The pulmonary leaflets appeared normal.

The left auricle was slightly dilated; its wall measured 4 mm. at the thickest portion. In contrast to the right auricular appendage, the left auricular appendage was small and the muscoli pectinati were not hypertrophied. The mitral valve was normal in appearance, except for slight marginal edema of the posterior leaflet. The chordae tendineae were thin and delicate. The papillary muscles and columnae carnae of the left ventricle were hypertrophied. The endocardium was opaque and grey in color. In the lower half of the septum the endocardium was greatly thickened, appearing as a yellowish grey layer. The myocardium in this area was not softened. The aortic leaflets were thin and delicate. In the musculature of the right auricle were numerous slightly opaque, yellowish areas, the largest of which measured 3 by 5 mm. The myocardium was of coarse texture. In the left ventricle, there was an occasional small grey area; yet everywhere throughout the heart the knife, as it cut, encountered unusual resistance, making an audible creaking noise.

In the interventricular septum, beneath the area where the endocardium was thickened, the muscle had been replaced by dense connective tissue, and near the margins of this connective tissue the muscle appeared slightly sunken and dark red, in contrast to the more greyish red muscle elsewhere. The alteration in the interventricular septum was very extensive and in one of the prominent columnae carnae, close to the posterior margin of the septum, were encountered areas which were opaque, yellow, and homogeneous. These were bordered by a narrow zone of hemorrhage. The scarring in the septum was quite marked, and large areas of fibrosis were seen, which obviously had followed previous patches of necrosis.

The coronary arteries were remarkably thin and delicate. About 1 cm. below its point of origin, the anterior descending branch of the left coronary was distended, and its lumen was filled for a distance of 1 cm. by a greyish red mass, which slipped

out with great ease, and was not attached to the wall at any point. No similar mass was found in any other branch of the coronary arteries.

There were numerous infarcts in both lungs.

Microscopic Examination—

Heart (Right Auricle and Left Ventricle): The muscle fibers were very irregular in arrangement and appearance. They were large in size. Most of them were vacuolated, and this feature in many places was so pronounced that only a little remnant of sarcoplasm remained against the cell membrane, mak-

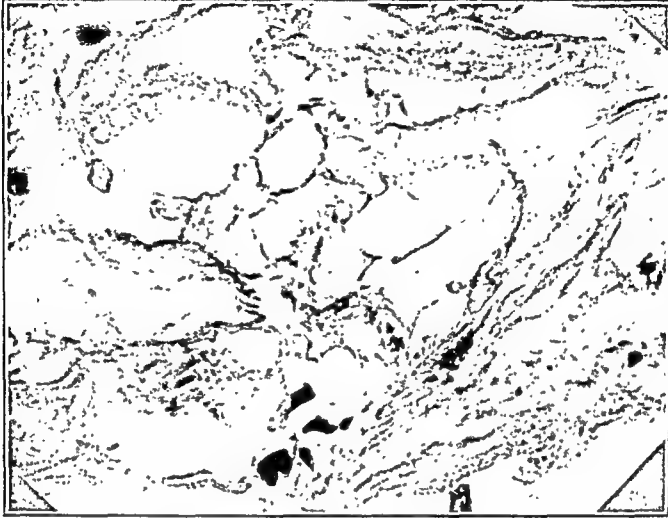


Fig. 5.—(Case 2) Hydropic degeneration of heart muscle fibers. Note the extreme vacuolization and almost total absence of sarcoplasm. Hematoxylin and eosin; $\times 720$.

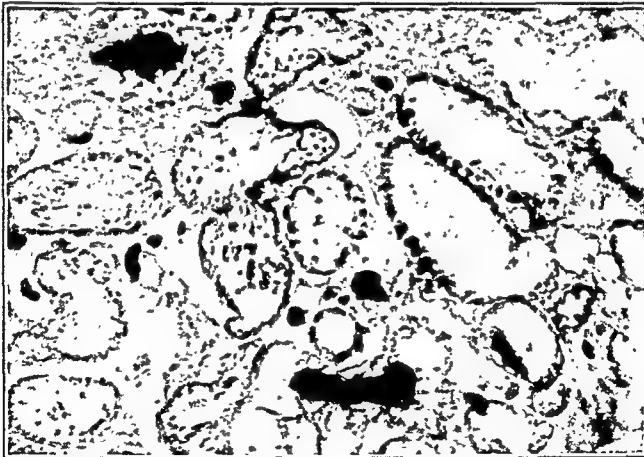


Fig. 6.—(Case 2) Hydropic degeneration of heart muscle fibers, most of which are cut transversely. Vacuolization is less marked than in Fig. 5. Hematoxylin and eosin; $\times 720$.

ing the muscle fibers appear as empty envelopes. The nuclei varied greatly in size. Many were exceedingly large and contained an unusual amount of chromatin; others had an hydropic or vacuolated appearance. The nucleolus in some of the nuclei was very prominent; in others, it had a pale, watery appearance, and occasionally was swollen and stained with eosin. The myofibrils, when seen, were very coarse. In many places were large amounts of connective tissue, which was compact and dense, with but few blood vessels in it.

Fat Stain (Scharlach R.): A small amount of fat was present within some of the muscle fibers, but the clear material in the muscle which gave the vacuolated appearance did not stain.

Interventricular Septum: The same vacuolization and enlargement of the muscle fibers was shown in this preparation. The nuclei were distinctly enlarged and very hyperchromatic. Many were vacuolated and apparently in the process of degeneration. An irregular scar, composed of moderately dense, vascular connective tissue, extended down from the endocardium into the muscle for a considerable distance. Its position suggested that it must interrupt the conduction system. In one area, there was a large mass of muscle undergoing necrosis. The nuclei had practically disappeared. The striations, however, could be vaguely seen. Large phagocytic cells with vacuolated cytoplasm were collected about the infarct and were penetrating into the necrotic muscle cells.

The clot in the right ventricle showed the typical structure of a thrombus.

The mass from the anterior descending branch of the left coronary artery proved to be a recent thrombus.

The aorta showed no intimal thickening. With the van Gieson stain, the elastic fibers appeared to be large and well preserved. The media and adventitia were

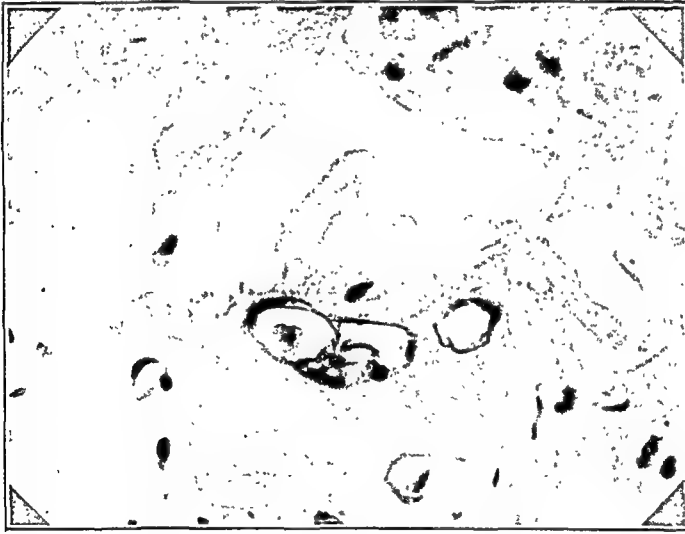


Fig. 7.—(Case 2) Nuclear degeneration of heart muscle fibers. The chromatin is concentrated at the margin of the nucleus. Hematoxylin and eosin; $\times 720$.

normal. The von Kossa stain for calcium was negative. There were no changes in any of the smaller vessels, including those in the kidneys.

Many of the alveoli of the lungs contained fresh blood and frequently groups of large mononuclear cells containing hemosiderin were collected in the alveoli. The capillaries of the septa were engorged, but did not bulge into the alveolar space, as in chronic passive congestion. The larger vessels were normal. The pleura was of normal width and appearance. In one section appeared a characteristic infarct.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; hydropic degeneration of the heart muscle; fibrosis of the myocardium; infarcts of the heart, old and recent; thrombi in the right ventricle; infarcts of the lungs; right hydrothorax; embolus of the anterior descending branch of the left coronary artery.

Final Note.—A case of extreme cardiac hypertrophy in a young man. The changes in the heart muscle were unique. The muscle had apparently undergone a marked hydropic degeneration, and a similar process affected the nuclei. No cause could be found to explain this. There were also recent and old infarcts and an embolus in the anterior descending branch of the left coronary artery.

CASE 3.—Unit No. 81293. G. T., colored male, married, aged thirty-one years, was admitted to the surgical service on May 10. He had been a rock-driller for ten years. He complained of a painful swelling in the right groin, which had been present for three weeks, and which he first noted two days after a drinking bout. There were no cardiac symptoms.

His mother died of heart trouble. He gave an indefinite history of "rheumatism" in the right hip fourteen years previously, which lasted for two weeks and never recurred. He had gonorrhea at fourteen. He had never had a serious illness. He smoked two packages of cigarettes a day and rarely took alcohol. He had been married for two years. There were no children.

It was noted that the heart was enlarged to the left, the apex impulse being seen and felt 12 cm. from the median line in the fifth space. The sounds were of poor quality, and a soft systolic murmur was heard at the apex. The blood pressure was 100/60. The Wassermann reaction of the blood was negative. The leucocyte

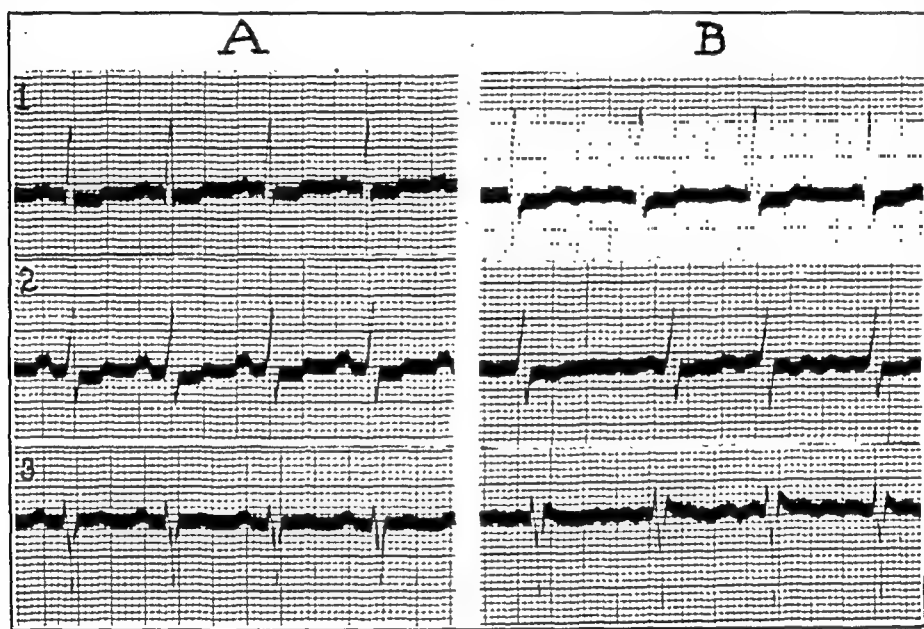


Fig. 8.—(Case 3) A. September 19, two weeks after the second admission to the hospital. Regular sinus rhythm, with rate of 94 and left ventricular preponderance. P-R (conduction) time is 0.15 second. The T-wave is inverted in Lead I, diphasic in Lead II and upright in Lead III. Three days previously digitalis, 0.8 gm., was given. Graphic signs of cardiac damage are relatively slight.

B. November 14 (six weeks before death). Auricular fibrillation, with rate of 72. There is but little change in the general form of the complexes.

count was 9,700, with 70 per cent polymorphonuclears. The urine contained neither albumin nor sugar. X-ray films of the chest showed no areas suggesting tuberculous infiltration, but the heart shadow was seen to be enormously enlarged, particularly to the left.

A mass of infected glands in the right inguinal region was incised and drained. Microscopic examination of a bit of tissue removed at operation showed no tubercles and no caseation necrosis. A definite diagnosis of tuberculous adenitis could not be made. The patient was discharged on May 19, with a granulating wound.

Two weeks later, he entered the city tuberculosis sanatorium, at Seaview, where he remained for two and one-half months. While there, an inguinal hernia was repaired. He gained ten pounds and was told that he did not have pulmonary tuberculosis. The night before he left this institution, he had his first attack of dyspnea,

and was unable to sleep because of difficulty in breathing. In spite of this fact, he soon returned to his job, but after working for one day he again had a sudden attack of shortness of breath, and was obliged to stop. Dyspnea continued, and palpitation and precordial pain appeared. On September 2 (three and one-half months after leaving the hospital and three days after resuming work), he was readmitted to the ward.

On admission, he was quite short of breath and looked ill. The temperature was 101.2° F. The left tonsil was moderately large, but did not appear to be infected. There were coarse râles scattered throughout both lungs. The heart was greatly enlarged to the left. The rate was 104. The rhythm was regular and the sounds of fair quality. There was a soft systolic murmur at the apex. The blood pressure was 98/72, but had risen on the following day to 106/86. There was slight clubbing of the fingers. The liver and spleen were not enlarged. Blood count showed: R.B.C. 4,260,000; hemoglobin 80 per cent; leucocytes 7,800, with 64 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. The sputum, on culture, yielded many influenza bacilli and numerous colonies of *Staphylococcus aureus* and nonhemolytic streptococcus. No tubercle bacilli were found at any time. The blood urea was 26 mg. per 100 c.c. Numerous blood cultures were negative. X-ray films of the chest showed patchy areas of density in the lower third of the right lung, suggesting pneumonic consolidation. The heart shadow was enormously enlarged. There was a good deal of peribronchial thickening, which was attributed to congestion of circulatory origin. The electrocardiogram showed sinus tachycardia, with rate of 120, and well-marked left preponderance. The P-R interval was 0.15 second. The T-wave was inverted in Leads I and II, and upright in Lead III. Inversion of T₁ and T₂ suggested myocardial damage (Fig. 8).

There was continuous elevation of temperature, with fluctuations from 98 to 104.8° F. There was also sustained tachycardia, the rate usually ranging between 90 and 110. Sinus tachycardia persisted until November 14, when auricular fibrillation, with rate of 72, was observed. Four days later, sinus rhythm reappeared. The leucocytes were never greatly increased, the highest count recorded being 12,000, with 85 per cent polymorphonuclears; they were usually under 10,000. There was no significant change in red cells or hemoglobin.

On September 12 (ten days after admission) he complained of sudden blindness in the left eye, and it was apparent that there had been an embolus in the central artery of the retina. Subsequently, expectoration of blood and pain in the left lumbar region suggested infarction of the lungs and left kidney. The blood pressure remained low—100 to 108 mm. systolic; 64 to 88 mm. diastolic. Aspirin, in large doses, appeared to have a mild antipyretic effect at times. The signs and symptoms of cardiac insufficiency gradually increased and were uninfluenced by digitalis, given at first in full dosage, and later as a maintenance ration. Congestive heart failure became extreme and a cardiac psychosis developed. He died on December 30 (4 months after admission), of advanced cardiac insufficiency.

Autopsy No. 10368.—The autopsy was performed by Dr. D. H. Andersen. On external examination, the striking feature was marked edema of the legs to the thighs, and also of the hands. The supraclavicular and axillary lymph nodes were moderately enlarged. There was slight clubbing of the fingers.

Thoracic Cavity: The pericardial sac contained 200 c.c. of clear, blood-tinged fluid. The heart occupied an area measuring 12 cm. in its vertical diameter, and 16 cm. in its transverse diameter. The right pleural cavity contained 900 c.c. and the left 400 c.c. of blood-tinged fluid.

Heart: The heart weighed 640 grams. The visceral pericardium was dull and there were a few small deposits of fibrin over both auricles and ventricles. These deposits were especially marked at the apex of the left ventricle. Over the upper,

anterior portion of the right ventricle, there was a white, opaque patch of thickened pericardium, about 2 cm. in diameter. The right auricle was not enlarged. The foramen ovale was closed save for a narrow, slit-like opening along the anterior margin. The tricuspid valve was composed of four leaflets, the extra leaflet being formed by the division of the marginal segment into two leaflets of approximately equal size. There was slight edema along the margins of the valve. There was thickening and lengthening of the chordae tendineae and moderate hypertrophy of the papillary muscle. The right ventricle was markedly dilated, especially in the region of the conus, below the pulmonary valve. There were thin streaks of endocardial thickening over the interventricular septum, and along the anterior wall of the ventricle. The interventricular septum bulged to the right. Numerous small, mural thrombi occupied the entire apex of the right ventricle. These appeared to be organized, and the subjacent muscle wall was thinned out. The left auricular wall was hypertrophied. There was slight, marginal thickening of the mitral cusps, particularly of the anterior leaflet.

The left ventricle was greatly hypertrophied and dilated, giving it an almost spherical shape. The endocardium of this chamber was thickened. Many small, adherent thrombi filled the interstices of the columnae carneae at the apex. The myocardium at this point was greatly thinned out. On section, fine fibrous strands extended from below the endocardium into the muscle.

The coronary arteries showed no changes, except for slight intimal thickening of the left branch.

The aorta and systemic arteries were normal. There were infarcts in the right lung, and in both kidneys. In a number of the inguinal lymph nodes were seen small areas of scarring.

The changes in the other viscera were those characteristic of chronic passive congestion.

Microscopic Examination—

Heart: The epicardium was slightly thickened. The muscle fibers were hypertrophied and their nuclei were irregular in shape, pale and uneven. Occasional small hemorrhages were observed separating groups of muscle bundles. Along the endocardium were seen old, completely organized and more recently formed thrombi. There was no evidence of acute inflammatory change in any of the sections. Gram and Levaditi stains showed no organisms.

The mitral valve was slightly thickened, due to edema. There was no cellular infiltration.

The coronary arteries, aorta and systemic vessels showed no changes.

An inguinal lymph node showed small areas in its center, which contained pinkish, necrotic tissue. At the margin was a ring of young fibroblasts, forming a layer of even thickness about the necrotic mass. Around the fibroblastic ring were lymphocytes. A few giant cells were seen in the zone of fibroblasts.

Anatomical Diagnosis.—Cardiac hypertrophy and dilatation; mural thrombi in the ventricles; infarcts of the right lung and both kidneys; chronic passive congestion of the lungs, liver, spleen, and pancreas; bilateral hydrothorax; hydropericardium; ascites; edema of the extremities; tuberculosis of the inguinal lymph nodes; chronic prostatitis; congenital malformation of the heart (patent foramen ovale and quadricuspid tricuspid valve).

Final Note (by Dr. A. M. Pappenheimer).—The central lesion at autopsy was an enlarged heart with parietal thrombi, but without any significant valvular or myocardial lesions. The changes in the other organs were those associated with embolism and infarctions from mural thrombi and with cardiac insufficiency. In view of the patient's history of ten years of rock-drilling, one might anticipate silicotic changes. The cough and the x-ray findings were in accord with this possi-

bility, but the sections of the lung offered no support for this diagnosis. The enlarged lymph nodes in the groin, for which the patient originally entered the hospital, contained structures which resembled tubercles, but this could not be proved. The cause for the cardiac dilatation and mural thrombosis remained undiscovered. There were no clear-cut inflammatory changes other than those associated with the organizing thrombi.

DISCUSSION

Clinical Picture.—These three cases presented certain features in common. The patients were young adult males, aged respectively eighteen, twenty-nine, and thirty-one years. Two were white, one was a negro. The symptoms of onset were palpitation due to cardiac irregularity in two, dyspnea and precordial pain in the third. The duration of illness from the onset of incapacitating symptoms to a fatal termination was less than a year in all. In two instances, brief attacks of arrhythmia had been noted several years previously. Death was due to rapidly progressive cardiac insufficiency in the two older patients and to coronary embolism in the young man, aged eighteen.

The heart was conspicuously enlarged in all. There were no signs of valvular disease. The blood pressure was normal or a little below the normal. There were no evidences of arterial or arteriolar sclerosis. In each patient there occurred embolisms to the viscera—to the lungs in all three, to the kidneys in two, and to the central artery of the retina in one. In one patient, as has been stated, a coronary embolus terminated life. At autopsy, it was apparent that the emboli originated from masses of thrombi which lay within the ventricles of the heart. Fever was present for varying periods preceding death, and was probably associated with visceral infarctions.

In two cases, tachycardia and other cardiac arrhythmias played a prominent rôle in the course of events. Frequent transitions from one rhythm to another were recorded in electrocardiograms, which at times showed bizarre complexes. In the third case, the form of the graphic records deviated relatively little from the normal, and a short paroxysm of auricular fibrillation was the only form of irregularity.

Pathology.—Examination of the three hearts at autopsy revealed a number of points of similarity, as well as certain individually characteristic lesions. In the gross, enormous hypertrophy was striking, the heart weights being 740, 750, and 640 grams, respectively. There were areas of myocardial softening in two cases, especially noticeable in the region of the interventricular septum. In places, the endocardium was thickened. Thrombi lay between the columnae carnae of the ventricles and bits of clot had evidently broken off with resultant embolism and infarction in the lungs and kidneys.

There were no vegetations on the heart valves, nor was parietal endocarditis present. The aorta, coronary, and systemic arteries showed no

changes. The kidneys appeared to be normal. In no instance was the thymus enlarged.

On microscopic examination, hypertrophy of individual muscle fibers was observed in all three cases. In two, infarcts of the myocardium were seen undergoing necrosis, as well as in various stages of degeneration and repair. In other sections there were numerous connective tissue scars, representing healed lesions.

As noted in the protocol, the heart muscle cells and their nuclei in Case 2 exhibited a curious hydropic degeneration, with extreme vacuolization. Similar changes have been observed in the myocardium of patients who have died of diphtheria.¹ In Case 3, only a few hemorrhages were seen between the bundles of hypertrophied muscle cells.

There were no inflammatory changes other than those associated with organizing thrombi. A diligent search was made for lesions suggestive of rheumatic fever, syphilis, or arteriosclerosis, but none were found.

Etiology.—The histories and clinical data afford no clues as to etiology. Even in the light of the post-mortem examinations, the cause for the cardiac enlargement and mural thrombosis remains obscure. With such imperfect knowledge, it is impossible to say whether these cases represent a single condition, perhaps at various stages of its evolution; or whether we are dealing with three persons whose hearts have reacted in similar, though not identical, fashion to entirely different harmful processes or agents. At present, it is difficult to bring into association the diverse lesions found in the myocardium on microscopic examination; yet similarity of many of the essential features, both clinical and pathological, lends support to the belief that the three cases may be regarded as bearing a relationship to one another.

A discussion of possible pathogenetic factors must, of necessity, be purely hypothetical and it is apparent that no definite conclusions can be formulated. The rôle of prolonged, violent exercise or of excessive fluid intake seems excluded by the histories. There were no abnormalities in the origin or distribution of the coronary arteries.

That the cardiac enlargement may be the result of a congenital anomaly is suggested by certain points of resemblance between these cases and instances of "idiopathic hypertrophy of the heart" in children, of which some fifty adequately described examples are on record. A number of these young patients have not manifested any symptoms until they were several years of age, and this, as Howland² has said, would make it seem possible if not probable, that the hypertrophy has been late in developing. In one of the children reported by him, there were no signs of cardiac disorder until the age of four. Most of these youngsters, however, have not survived for many months, and the final catastrophe has been of short duration, a matter usually of a few days or weeks. Examination of many of the hearts at autopsy has shown

but little other than hypertrophy of the fibers; and some observers would exclude from the group those cases exhibiting further changes in the heart muscle. In a number of instances in which the established criteria were otherwise satisfactorily met, lymphocytic infiltrations between the muscle bundles have been found. In more recent accounts there have been described, in addition, areas of degeneration and necrosis in the myocardium, with replacement fibrosis and endocardial thickening;^{3, 4} hydropic degeneration of the heart muscle cells;⁵ and vacuolization of these cells, which was regarded as distinctly abnormal and of unknown origin.⁶

In our own cases it is conceivable that the condition, if the result of congenital predisposition, may not have developed until later in life. How long hypertrophy was present prior to the onset of discomfort, is not known. The rapid increase in the severity of the symptoms, as well as the character and extent of the lesions at autopsy, point to a progressive process. It is of interest to note that minor congenital malformations were present in two of our patients; namely, a common origin of the innominate and left common carotid arteries, and anomalous fissuration of the lungs in Case 1; partial patency of the foramen ovale and a quadricuspid triicuspid valve in Case 3.

Whereas at the bedside an infectious origin was suspected, no evidence in support of this notion was present at autopsy. The resemblance of the hydropic degeneration of the muscle fibers to the lesions sometimes found in diphtheria has already been mentioned. No lead was obtained pointing to any specific causative bacterial agent or virus; and the usual changes associated with inflammation were conspicuously absent. There were no cellular infiltrations such as characterize acute interstitial myocarditis of the Fiedler type.

In a search of the literature, only two cases were encountered which might be regarded as bearing some resemblance to those here described. Laubry and Walser⁷ observed a robust youth, aged fifteen years, who died suddenly within three months after the onset of anorexia and dyspnea. There was no history of antecedent disease. The symptoms of cardiac insufficiency were rapidly progressive and were unresponsive to the usual therapeutic measures.

At autopsy, the heart weighed 490 grams. The myocardium was pale and flabby. There were no valvular lesions or intracardiac thrombi. A large infarct was present in the lower lobe of the right lung. The aorta was normal. Microscopically, the heart muscle showed only a mild degree of interstitial edema. There were no pathological changes in the other organs.

To this form of cardiac insufficiency without apparent cause, Laubry applied the term "myocardic." Walser⁸ again reported the same case in the monograph submitted for his thesis and endeavored to enlarge

upon the concept. But he added no relevant clinical material controlled by post-mortem examination.

The second case was described by Whittle.⁹ A twenty-year-old student at Cambridge, England, suddenly fell dead while riding his bicycle. Post-mortem examination revealed a huge heart, which weighed 840 grams. The valves, endocardium, and coronary arteries were normal. The thymus weighed 30 grams. The aorta was quite delicate and of small caliber, measuring 16 mm. at the beginning of the descending portion (the average normal aorta at this level measures 23 mm.). There were flecks of early atheroma near its origin. An acute tracheitis was present. Microscopic examination of sections of the left ventricle showed cloudy swelling, with loss of regular striation of the fibers. There were no foci of necrosis, degeneration, or inflammation. The kidneys were normal. There were no changes in the systemic arteries or in the arterioles of the viscera.

The history revealed little. He had been healthy and lived a normal life. He had done much cycling over long distances, but no racing. There was no evidence of indisposition prior to death. The level of the blood pressure was not known.

The great size of the heart remained entirely without explanation. The large thymus and hypoplastic aorta were not considered to be primary causative factors. Cloudy swelling of the heart muscle fibers was ascribed to a toxic effect of the acute tracheitis. Whittle regarded the prolonged muscular exertion of cycling as an important element in inducing the cardiac hypertrophy. But such an interpretation of the facts leaves many obvious questions unanswered.

Diagnosis.—During life, prominence of the cardiac manifestations in all three cases suggested rheumatic fever as the most likely etiological diagnosis. Elevations of temperature, systolic murmurs, and frequent changes in the form of the electrocardiogram tended to support this idea. In the first case, because the patient had lived in South America, diagnostic consideration was given to the cardiac form of American trypanosomiasis, as described by Chagas. In this case also, coronary disease and syphilis were mentioned as the basic pathological states. In the third patient, clubbed fingers and the numerous embolic phenomena brought up the possibility of subacute bacterial endocarditis. This man was a negro and biopsy of an enlarged inguinal gland showed structures resembling tubercles; hence, it was inferred that tuberculous pericarditis might be present, perhaps with adherent pericardium. He had also been a rock-driller for ten years. It was not unreasonable to suspect silicotic changes in the lungs, to which the cardiac disturbances were secondary.

For the present, the diagnosis, if made during life, must be arrived at by exclusion. It is not known whether these cases are unrelated in their pathogenesis or represent different phases of a single disease

process. In the absence of such knowledge and of the etiology, it would serve no useful purpose at this time to attempt to define diagnostic criteria. It is hoped that further observations will throw added light on this unusual form of cardiac enlargement.

SUMMARY

Three cases have been described presenting an unfamiliar clinical picture. The main features were great cardiac enlargement, intra-ventricular thrombosis with embolisms to the viscera, and death within a year after the symptoms were well established. There were no signs of valvular disease or arteriosclerosis, and the blood pressure was at the normal level or slightly below it. Microscopic examination of the myocardium showed hypertrophy of muscle fibers in all, infarcts in varying stages of degeneration and repair in two, and in one of these, a curious hydropic degeneration of the heart muscle cells with vacuolization of the sarcoplasm. The third case showed only a few hemorrhages between the muscle bundles. No inflammatory changes or signs of arteriolar disease were observed.

Though clinically the patients presented many essential features in common, the lesions at autopsy were not identical. It was not possible to state whether these cases represented a single condition at different phases of its development or were entirely unrelated in their pathogenesis. The etiology remained obscure.

REFERENCES

1. Eppinger, H.: Die toxische Myolyse des Herzens bei Diphtheritis, *Deutsch. med. Wehnschr.* 29: 257, 1903; also, Roman, B.: Extensive Diffuse Hydropic Degeneration of the Myocardium. Associated With a Diphtheritic Infection, *Bull. Buffalo Gen. Hosp.* 7: 29, 1929.
2. Howland, J.: Idiopathic Hypertrophy of the Heart in Young Children, *Contributions to Med. and Biol. Research Dedicated to Sir William Osler*, 1919; 1: 582 (P. B. Hoeber).
3. Stoloff, E. G.: So-Called Idiopathic Enlargement of the Heart in Infancy and in Childhood, *Am. J. Dis. Child.* 36: 1204, 1928.
4. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children, *Am. J. Dis. Child.* 45: 828, 1933.
5. Steiner, M., and Bogin, M.: Idiopathic Cardiac Enlargement Associated With Status Thymicolymphaticus, *Am. J. Dis. Child.* 39: 1255, 1930.
6. Sprague, H. B., Bland, E. F., and White, P. D.: Congenital Idiopathic Hypertrophy of the Heart: A Case With Unusual Family History, *Am. J. Dis. Child.* 41: 877, 1931.
7. Laubry, C., and Walser, J.: Sur un Cas d'Insuffisance Cardiaque Primitive; Les Myocardies, *Bull. et mem. de la Soc. des Hôp. de Paris* 49: 409, 1925.
8. Walser, J.: La Myocardie; Syndrome d'Insuffisance Cardiaque Primitive, 1925, Paris, Librairie Octave Doin.
9. Whittle, C. H.: "Idiopathic" Hypertrophy of the Heart in a Young Man, *Lancet* 216: 1354, 1929.

THE HEART IN MYXEDEMA, WITH A REPORT OF TWO CASES*

PHILIP HALLOCK, M.D.

MINNEAPOLIS, MINN.

SINCE the original observations of Zondek¹ in 1918 on the so-called myxedema heart, considerable literature has accumulated describing the cardiac sequences resulting from the myxedematous state. From the studies reported by various authors conflicting opinions have arisen concerning the extent of damage to the heart in the course of the disease. Although several authorities have questioned the very existence of a cardiac syndrome associated with myxedema, it is now well established that protracted cases in some instances will produce gross signs of myocardial insufficiency. The controversy appears to be centered about the question of the frequency of heart failure in myxedema. Lerman, Clark and Means² are of the opinion that congestive failure in myxedema is rare, while Fahr³ contends that the incidence of heart failure associated with the disease is high.

Because of the inconstancy of heart failure in reported cases of myxedema, I have approached the study of the problem from an angle somewhat different from that of previous investigators in an attempt to determine when true heart failure exists in myxedema. The opportunity for the study was afforded by two typical cases of myxedema in each of which the outstanding symptom was dyspnea. Case 1 presented the findings of a gross congestive failure of a moderate degree. In Case 2 this feature was entirely lacking; yet further studies indicated that myocardial insufficiency was actually present.

REVIEW OF LITERATURE

As already mentioned, myxedema heart was first recognized as a clinical entity by Zondek¹ in 1918 who reported four unusual cases of myxedema in which he could demonstrate cardiac enlargement with sluggish cardiac movements, accompanied by bradycardia and alterations in the electrocardiogram. He not only demonstrated the existence of a generalized cardiac dilatation but also observed a remarkable diminution in the transverse diameter of the heart and a return of the electrocardiogram to its normal contour following the administration of thyroid extract. A reduction of 5.7 cm. in the transverse diameter of the heart was noted in one of his cases after eight weeks of thyroid therapy. Since his original observation, corroborative evidence has accumulated in the literature to justify the term myxedema heart as a

*From the Department of Medicine, University of Minnesota and Minneapolis General Hospital.

distinct clinical entity in heart disease. Thus Assman⁴ in 1919 reported a case of myxedema heart, the findings in which conformed in all respects to those of Zondek. This observer showed that digitalis was ineffective upon the heart failure in myxedema. However, when thyroid therapy was instituted in this case, marked clinical improvement of the myxedema and of the heart failure was noted. The transverse diameter of the heart decreased 4 cm. In 1920 Meissner⁵ reported three cases of myxedema. Following thyroid therapy there was a shrinkage of 4.5 cm. in the transverse diameter of the heart as shown by the teleroentgenogram. The second case was complicated by a chronic nephritis with a systolic pressure of 180. After two months of thyroid therapy, a marked clinical improvement was observed, although subsequent x-ray studies showed no actual shrinkage in the size of the heart. The third case studied showed no cardiac enlargement. In 1924 Laubry, Mussio-Fournier and Walser⁶ reported a case of myxedema associated with anginal attacks. Orthodiagraphic studies disclosed cardiac dilatation. Again in this case, when digitalis was administered, no relief was noted, but when thyroid medication was initiated, marked clinical improvement with a reduction in the size of the heart was soon apparent. In 1925 Fahr⁷ reported three cases of myxedema. In his first case, he showed that the administration of digitalis, rest in bed, and fluid restrictions had very little therapeutic effect in ameliorating the symptoms and signs of heart failure. However, when thyroid therapy was instituted, the signs of congestive failure promptly cleared up. In one of his cases, after a period of seven weeks under thyroid treatment, the transverse diameter of the heart decreased from 19 cm. to 12.7 cm. The electrocardiogram, which originally showed a left axis deviation, negative T₁, and iso-electric T₂ with a QRS spread of 0.18 sec., also became normal. He was further able to show that after the withdrawal of thyroid, not only did the signs of myxedema reappear, but also that the heart again dilated so as to produce signs of cardiac insufficiency. Curschman⁸ in 1926 also described a case of myxedema with cardiac dilatation and congestive heart failure which responded readily to thyroid medication. In 1929 Duden⁹ reported a case of myxedema with myocardial failure which disappeared following the administration of thyroid. A recession of 3.5 cm. in size of heart was observed after a period of six weeks. In 1931 Davis¹⁰ confirmed the results obtained by Fahr. He reported that after the restoration of the heart to its normal size under thyroid regime, the heart would dilate and signs of congestive failure reappear if thyroid was withdrawn. He showed further that the heart would again return to its normal size, with the disappearance of heart failure, upon the readministration of thyroid. This he could not accomplish with digitalis. This phenomenon of dilatation and return to normal suggested to Dr. Moses Barron¹¹ the term "accordion heart."

Cases of myxedema without congestive failure but with diffusely dilated hearts have been reported. Zins and Rösler¹² in 1926 were able to demonstrate a shrinkage of 3.3 cm. in the transverse diameter of the heart after three weeks of thyroid therapy. Similarly, Schittenhelm and Eisler¹³ in 1927 reported a reduction in the transverse diameter of the heart from 18 cm. to 14.7 cm. in a period of eleven days after intravenous administration of 12 mg. of thyroxin. The electrocardiogram also returned to normal in this short period. In 1929 Holzman¹⁴ reported a case very similar to that reported by Meissner⁵—that of a man fifty-eight years of age who presented the typical signs and symptoms of myxedema. The heart was enlarged both to the left and to the right as seen in the x-ray film, while the electrocardiogram showed a low voltage in all leads with left axis deviation and abnormal QRS complexes in all leads. Marked clinical improvement of the myxedematous state was observed following adequate dosage of thyroid, yet no demonstrable changes were noted in the graphic records, nor was there any appreciable reduction seen in the x-ray outline of the heart.

The existence of the cardiac syndrome of myxedema heart has been challenged by several authorities. Christian,¹⁵ in a comprehensive study of thirty cases of myxedema in 1925, was unable to find a single case which exhibited evidence of congestive failure with a picture of a generalized cardiac dilatation as described by Zondek, Assman and Fahr. Willius and Haines,¹⁶ after studying 162 cases of myxedema with particular reference to the status of the heart in myxedema, were unable to justify the establishment of a cardiac syndrome of myxedema. Means, White and Krantz¹⁷ studied forty-eight cases of myxedema with special reference to the cardiac signs. They found only one case which showed the classical signs of cardiac dilatation and T-wave negativity as described by Zondek. While they admitted that myxedema heart existed, they emphasized the rarity of the condition. Case,¹⁸ in an analysis of 58 cases of myxedema, could not find a single one corresponding to Zondek's description. Ayman, Rosenblum and Falcon-Lesses¹⁹ reported two typical cases of myxedema showing the classical signs of cardiac dilatation with changes in the electrocardiogram, but found no evidence of cardiac insufficiency. Lerman, Clark and Means² in a recent study in a series of thirty cases of myxedema were able to find only one case which showed evidence of gross congestive failure. However, they point out that four cases showed evidence suggestive of cardiac failure. One case showed crepitant râles at the lung basis and pitting edema of the extremities and the sacrum. The second case showed a small amount of fluid in right pleural cavity, pitting edema, and the liver palpable at the costal margin. The other two cases revealed crepitant râles at the lung basis, palpable liver edge, and pitting edema. All of these signs disappeared on rest and thyroid medication. Yet, they do not consider these findings conclu-

sive evidence of myocardial insufficiency as a direct result of the myxedematous state. They are of the opinion that the patients who present findings suggestive of cardiac failure usually have a coexisting hypertension and arteriosclerosis. Means²⁰ remarks that while the phenomena of congestive failure are rare, the characteristic enlargement described by Zondek is commonly seen. In the Massachusetts General Hospital series of thirty cases, twenty-seven under thyroid therapy showed some shrinkage in size as determined by roentgenological examination. Therefore, Means concludes, in view of the fact that some degree of dilatation is almost always present, that cardiac enlargement should be considered a part of the picture of myxedema rather than a complication.

On the other hand, Fahr,³ in a recent study of seventeen cases of myxedema heart, concluded that 75 per cent showed some signs and symptoms of heart failure, while 30 per cent showed very severe evidence of congestive failure. Tung,²¹ in an analysis of eighteen cases of myxedema, found seven cases (39 per cent) which showed signs of cardiac insufficiency. Thus there appears to be a considerable discrepancy in the incidence of heart failure in myxedema as reported by the various authors.

However, in the analysis of these Massachusetts General Hospital cases,²⁰ 65 per cent of the series showed dyspnea. This agrees very well with the report of Ayman and his associates who found that of twenty-two cases analyzed from the literature, 60 per cent showed shortness of breath. Whether or not dyspnea should be interpreted as a cardinal symptom of congestive failure in cases of myxedema is, of course, a matter for argument. If it were possible to analyze the dynamic events as cardiac dilatation manifests itself, it would probably be found, as Wiggers²² believes, that the degree of dyspnea is roughly related to the decreasing efficiency of the heart. In this event, the percentage of heart failure, in the strict sense of the term, would obviously be too low in the Massachusetts General Hospital series.

CASE REPORTS

CASE 1.—White female, aged fifty-six years. Chief complaints were increasing weakness and fatigue and marked dyspnea on exertion. She dated the onset of her illness approximately six years ago. At that time, her first symptom was weakness, which steadily progressed. This was accompanied by gradual loss of ambition. She was seen then by a physician and was told that she had high blood pressure. In the past four years, her skin had become dry and scaly with a loss of hair. She also noted that she began to increase in weight in spite of the fact that her appetite was poor. During the past two years, she noted that her voice gradually became coarser and deeper in pitch. Her tongue was "always in the way" when she wanted to talk. Some impairment of hearing was noted at this time. She felt cold constantly, even during the hot summer days. For the past two years she visited a physician because of rheumatic pains in her knee joints and right shoulder. The medication given offered no relief. A bloated feeling in her abdomen bothered her

constantly. For the past year, she was forced to abandon her social activities and housework because she was becoming so sluggish and clumsy. Her memory became poor, and she appeared to take no interest in life. Especially during the last year she noted that she was becoming short of breath. It was almost impossible for her to climb the stairs and do her housework because the slightest exertion would compel her to stop and gasp for breath. During the past half year, she noticed that her ankles and legs were swollen. There was no history of thyroidectomy or thyroiditis.

Physical examination revealed a typical case of myxedema. The patient appeared listless and apathetic. Cerebration was retarded. Articulation was slow. The voice was deep and of a monotonous character. The palpebral fissures were markedly narrowed with puffy, boggy lids. The nose was broad and thick. The lips were thick and had the appearance of a reddish cyanosis. The complexion was pale and waxy with a circumscribed pinkish flush over the malar prominences. The hair was sparse and brittle. Bolsters of supraclavicular fat were present on both

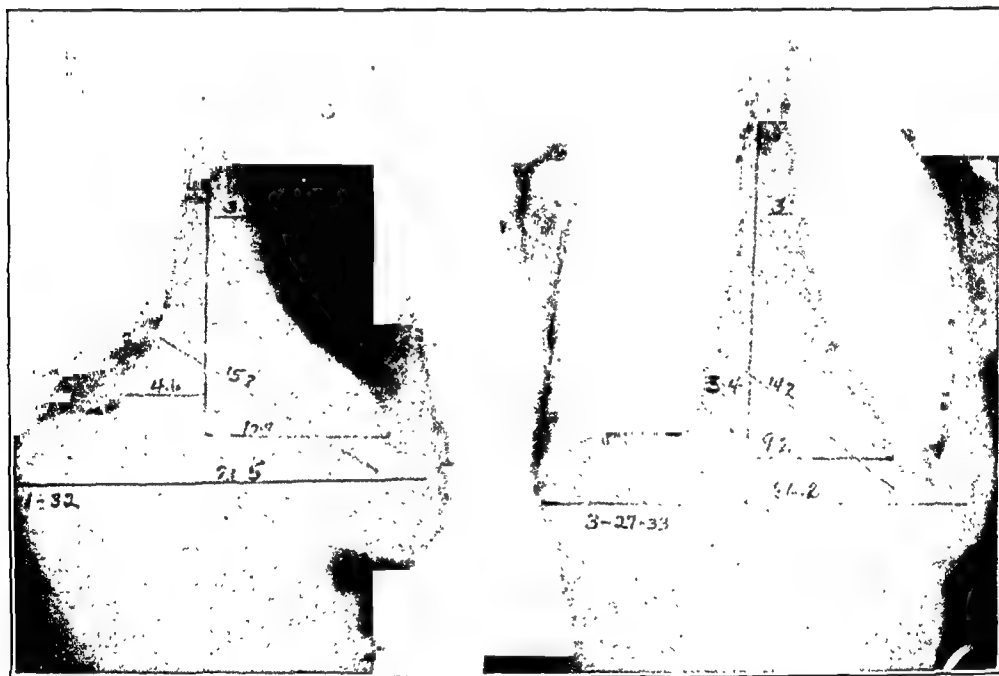


Fig. 1.—Case 1. Appearance of teleroentgenogram before and after five and one-half months of thyroid therapy. Before treatment: basal metabolic rate -36 per cent; blood pressure 160/110 mm. After five and one-half months of therapy: basal metabolic rate -4 per cent; blood pressure 135/98 mm.

sides. The skin felt cold and was thick and dry. Dyspnea on the slightest exertion was evident. The heart tones were faint. The pulse rate was 68. No murmurs were elicited. Râles were present over bases of both lung fields. The liver was palpable at the costal margin in the midclavicular line. No ascites was noted. Considerable pitting edema of the lower extremities was present. No varicosities were found. The vital capacity was 2200 c.c. The patient weighed 187 lb. Wassermann and Kahn tests were negative. Hgb. 66 per cent; R.B.C. 3,280,000; W.B.C. 6,800; P.M.N. 70 per cent; Lymph. 24; Mono. 5; Eos. 1. Urine showed a specific gravity of 1.025 with faint trace of albumin and 0-1 pus cells, and occasional hyaline casts. The plasma protein determination was above normal. B.M.R. 36 per cent. Blood pressure 160/110 mm. Six-foot plate of the heart showed a diffusely dilated heart, Ml—10.9 cm.; Mr—4.6 cm.; T—15.5 cm. Transverse thoracic diameter—26.5 cm. (Fig. 1.) The graphic record on admission (Fig. 2)

demonstrated a tendency to a right axis deviation, isoelectric T_1 with slightly positive P_1 , diphasic T_2 and diphasic T_3 . The QRS spread in all leads was 0.1 sec. and therefore just at the upper limits of normal. Eyeground examination showed a minimal degree of retinal arteriolosclerosis. The patient was started on 1.5 gr. of thyroid extract (Armour's) daily, and on the third day, the amount was raised to 3.5 gr. Fluids were not restricted and the patient was not put to bed.

Definite changes were observed in the graphic records one week after the institution of treatment (Fig. 2). The downward deflection of the S-wave in Lead I had returned to the normal position; the diphasic T_2 and T_3 had become definitely positive. Graphic records taken approximately one and one-half months after treatment showed a positive T in all leads, and this could be interpreted as a normal electrocardiogram.

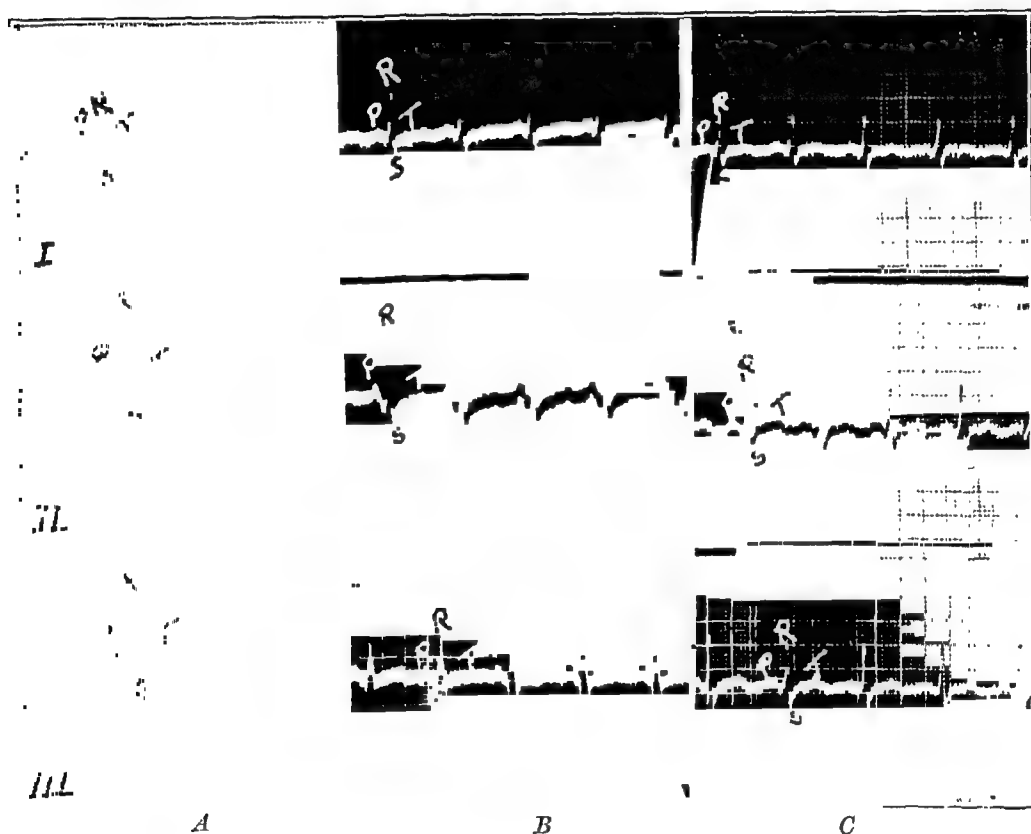


Fig. 2.—Case 1. Electrocardiographic changes: (A) before institution of thyroid therapy; (B) one week after the institution of treatment; (C) six weeks after the institution of treatment.

Teleroentgenograms showed a definite decrease in size of the cardiac shadow approximately one month after treatment. By this time a shrinkage of 1.7 cm. in the transverse diameter of the heart had occurred. It will be noted that the shrinkage occurred mainly on the right side of the heart. This is consistent with the QRS change in Lead I which occurred as early as one week after treatment. After five months of treatment, there was a total diminution of 2.9 cm. in the transverse diameter of the heart (Fig. 1).

It is also of interest to correlate the blood pressure changes with the return of the heart to its normal size. The initial blood pressure which was 160/110 mm. dropped to 140/90 mm. after one month, and to 135/85 mm. after two months of treatment. Since then it has varied slightly with the last reading. Duden⁹ in 1931 reported a similar finding in a case of myxedema with myocardial insufficiency.

Before treatment, the blood pressure was recorded as 180/130 mm. After treatment, with the disappearance of the sign of congestive failure, the blood pressure dropped to 130/85 mm.

The initial B.M.R. which was -36 per cent (checked) rose to -16 per cent after four weeks, to -9 per cent after eight weeks and to -3 per cent after twelve weeks of treatment. The weight loss in six weeks was 21 pounds, from 185 to 164 pounds. The vital capacity which was 2200 on admission changed to 2600 during the same period of time.

The case has now been followed for six months. At the end of the first six weeks, marked changes were already obvious. However, a slight amount of pitting edema was still present. The marked dyspnea on exertion, as well as the pitting edema, which the patient presented when first seen, had entirely disappeared after four months of treatment. Five months after treatment, it was no longer difficult for the patient to do her housework, to climb stairs or to take long walks. Her weight now was 144 pounds. The day before her last visit to the hospital she had done a large washing, and had sawed ten pieces of cord wood.

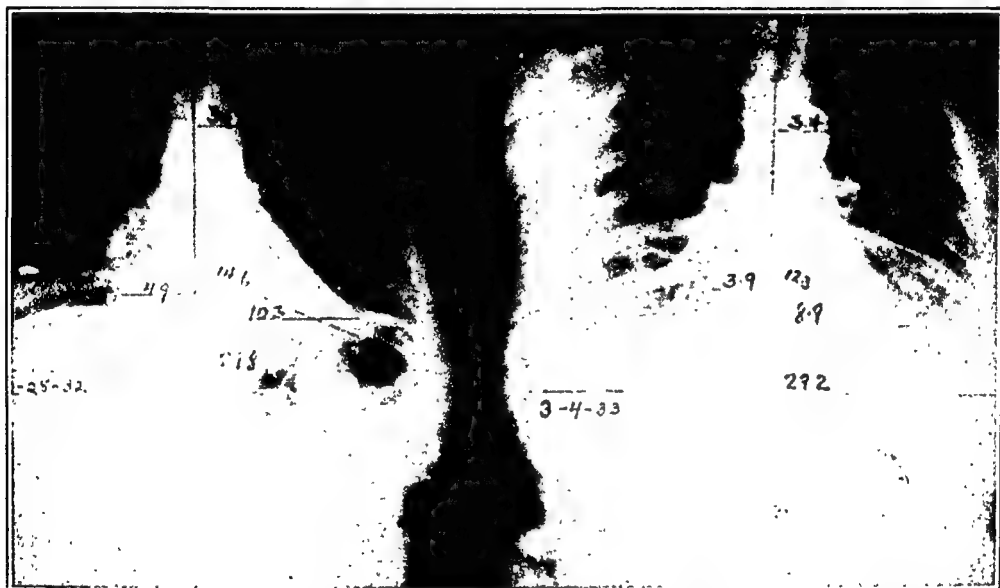


Fig. 3.—Case 2. Appearance of teleroentgenogram before and after two months of thyroid therapy. Before treatment: basal metabolic rate -30 per cent; blood pressure 130/90 mm. After two months of therapy: basal metabolic rate -4 per cent; blood pressure 130/70 mm.

CASE 2.—White female, aged fifty-six years. Chief complaints were fatigue and dyspnea on exertion. Onset of trouble began about two years ago with occipital headaches and development of a "tired feeling." Then she became constipated and began to gain weight. About eight months ago, she noticed a change in voice and swelling of the face, especially around the eyes. Her skin became very dry and rough, and her hair became dry and began to fall out. Her physician treated her for nephritis without relief. During the past few months, she noticed rapid development of fatigue and impairment of memory. Her normal weight of 145 had increased to 174 pounds. She could walk only a block or two before becoming exhausted. She had difficulty in doing her simple housework. Climbing the stairs in her house was almost an impossibility because of shortness of breath. She had no history of thyroidectomy or thyroiditis. A cholecystectomy had been performed nine years ago and tonsillectomy four years ago.

While this patient did not present the classical array of signs of myxedema as in Case 1, yet there was sufficient evidence to establish a diagnosis by physical examination. There was considerable puffiness around the eyes, with moderate narrowing of the palpebral fissures. Her voice was deep and coarse and her speech was slow. There was a masklike appearance of the face. Mental torpor was not evident as in the previous case. The skin was dry and rough, but not markedly thickened. Heart tones were faint. Her temperature was 97° F. and her pulse rate 64. Weight 175 pounds. Blood pressure 130/90 mm. Basal metabolic rate -30 per cent.

The lung fields were clear. The liver was not palpable. No ascites was present. No pitting edema of lower extremities noted. The blood pressure was normal. Hgb. 90 per cent; W.B.C. 5,500. Wassermann reaction negative. Kidney concentration test showed good renal function. Very faint trace of albumin was present in the urine with 18-20 pus cells per microscopic field. Blood urea nitrogen 18.9 mg. per 100 c.c. Vital capacity 2400 c.c. Eyeground examination showed no

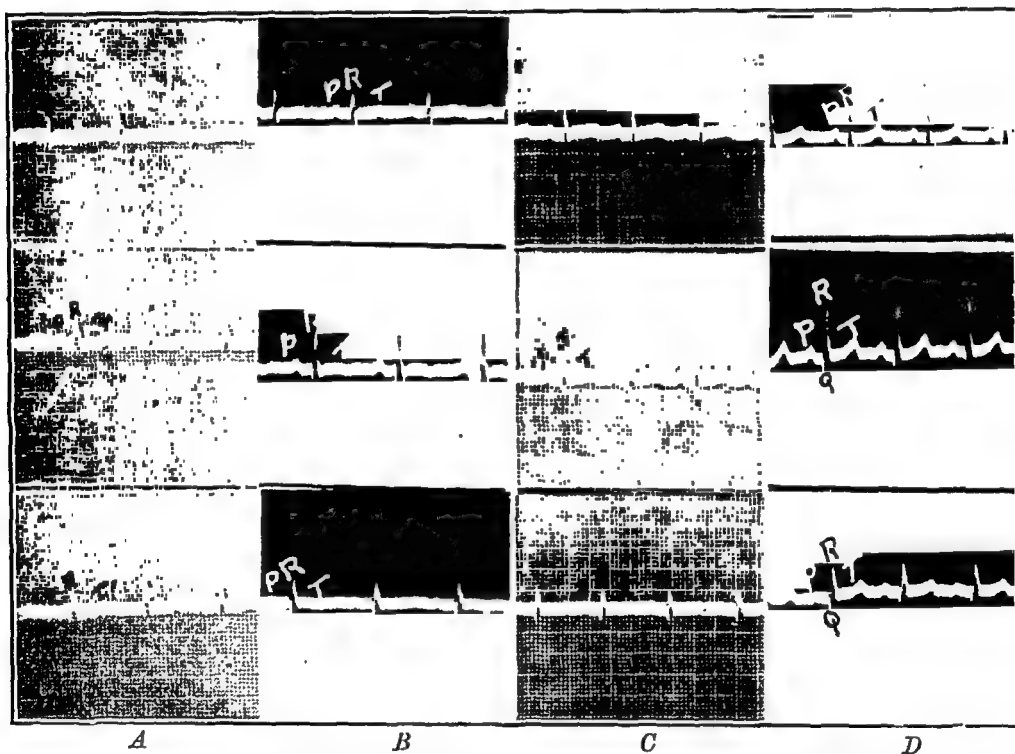


Fig. 4.—Case 2. Electrocardiographic changes: (A) before the institution of thyroid therapy; (B) nine days after the institution of treatment; (C) two weeks after the institution of treatment; (D) eight weeks after the institution of treatment.

arteriolar changes. The graphic record (Fig. 4) showed low voltage in all leads (under 5 mm.) with slightly negative T_1 . The six-foot plate showed a diffusely dilated heart, Ml—10.3 cm.; Mr—4.9 cm.; total diameter—15.2 cm. Total transverse thoracic diameter—29.8 cm. (Fig. 3). The patient was placed on 1.5 grains of thyroid extract daily, and on the third day the dosage was raised to 4 grains.

Graphic record (Fig. 4) taken nine days after institution of thyroid therapy showed an increase of 3.5 mm. in the amplitude of the QRS complex in Lead II. After two weeks of therapy the T_1 became positive. After eight weeks of treatment, the height of the T-waves as well as the amplitude of the QRS complexes increased in all leads. Appreciable changes in the size of the cardiac shadow were noted after a period of a month. Thus the transverse diameter of the heart regressed 1.7 cm. At the expiration of two months, the total shrinkage in the transverse diameter of the heart was 2.4 cm.

A slight variation was noted especially in the diastolic pressure. On admission, the blood pressure was 130/90 mm.; after the first month 125/75 mm.; and at the end of the second month 130/70 mm. This, together with the blood pressure changes noted in Case 1, is in accord with the variations reported by the Boston investigators² who observed a drop of 10 mm. or more in the diastolic pressure in fourteen cases following the administration of thyroid. The rise in the basal metabolic rate was striking. The basal metabolic rate changed from a -30 per cent to -4 per cent (checked) in period of one month.

Before the institution of thyroid therapy, the minute volume was 3.4 liters.* It was checked the following day and the value was 3.6 liters. After two months of thyroid treatment, the minute volume had increased to 4.4. The initial vital capacity which was 2400 c.c. rose to 2600 c.c. after a month of treatment. This is in close agreement with the findings of Blumgaard and his associates²³ who found no significant changes in the vital capacity after thyroid treatment. In their series of cases of myxedema not one showed gross evidence of congestive failure.

This case has been followed for two months. The patient's dyspnea has entirely disappeared, and she can now carry on her routine housework without the slightest difficulty.

THE INTERPRETATION OF ELECTROCARDIOGRAPHIC CHANGES IN MYXEDEMA

The absence of the thyroid hormone may give rise to a number of disturbances in the cardiac conductive mechanism. That these graphic manifestations are not due to intrinsic alterations in the myocardium but rather to an impairment in the electrical conductivity of the myxedematous skin was the contention first advanced by Leug.²⁴ Nobel, Rosenblüth and Somet²⁵ were also of the opinion that increased resistance due to myxedematous infiltration in the skin and subcutaneous tissue could explain some of the alterations in the graphic records. It appears from recent work that such is not the case. The contour, time relations and amplitude of the auricular and ventricular complexes are fundamentally initiated in the heart and are not expressions of pathological changes in the skin. In order to determine whether the T- and P-wave alterations occurred in other abnormal skin conditions, I studied the graphic records of a case of generalized scleroderma—a condition in which there is profound infiltration in the skin and subcutaneous tissue. In this case the T- and P-wave deflections were of normal contour and amplitude. Likewise, in two cases of generalized ichthyosis, the T- and P-waves showed no abnormal alterations. However, it remained for White,²⁶ who employed needle electrodes, to show conclusively that the altered conductivity of the myxedematous skin had no influence on the graphic records. Reid and Kenway²⁷ have shown further that lower metabolic rates themselves, without myxedema, cannot give rise to definite electrocardiographic changes. True myxedema must be present to have the characteristic changes. The preponderance of evidence therefore supports the origi-

*The writer is indebted to Dr. A. C. Kerkhof who performed minute volume studies in Case 2, using the acetylene gas method of Grollman.

nal conception set forth by Zondek¹—that the fundamental changes are essentially a result of a disturbance in the conductive mechanism of the heart.

The most frequent alterations seen in the electrocardiogram in myxedema heart are the flattening and the inversion of the T-waves which are usually seen in Leads I and II. Twenty-three out of twenty-four cases from the Massachusetts General Hospital¹⁶ showed a low T-wave, while nine showed low voltage, and abnormal axis deviation. In Fahr's series³ the majority of cases showed negative T-waves in Leads I and II. Thacher and White²⁸ in a series of fourteen cases showed a flattening of the T-waves in Lead I in all of their cases. The P-R intervals in these cases were usually normal, while the QRS complexes in several instances showed a low potential. They also observed a marked correlation between the height of T-waves and the level of basal metabolic rate. By no means are the changes limited to the T-waves. Zondek¹ found low and absent P-waves. Ziskin²⁰ in 1930 reported a case which showed a delayed P-R interval. The case reported by Davis¹⁰ showed not only a flat P- and T-wave, but also a prolonged P-R interval varying from 0.20 sec. to 0.22 sec. In this same case, the axis deviation was normal before thyroid therapy, but after thyroid, the patient developed a left axis deviation. Tung,²¹ after a study of 18 cases of myxedema, found P- and QRS waves of relatively small amplitude. However, the most striking abnormality in Tung's series was a flattening and inverting of the T-waves. After thyroid treatment, these abnormalities disappeared in the graphic record of 7 cases. In the case reported by Gardner³⁰ an abnormal spread of the QRS₁ was noted which returned to its normal limits under thyroid treatment. In my cases reported above, the electrocardiographic changes were striking. Case 1 showed an abnormal downward deflection of the S-wave in Lead I, and iso-electric T₁ and a diphasic T₂. After a week of thyroid extract, the graphic record showed a normal axis deviation and an upright T₂. The T₁ which was still iso-electric became positive after two weeks of thyroid therapy. In Case 2, before treatment, the graphic record showed a low voltage in all leads with a flat T₁. The only change noted after a week of thyroid therapy was an increase in amplitude, particularly in Lead II where the voltage increased 3 mm. After a period of two weeks, the T-waves in Leads I and II were definitely positive. It was interesting to note in the serial study of the graphic records in Case 2 the progressive increase in height of the T-waves, especially in Leads I and II. That such a condition obtains in normal individuals has recently been shown by McGuire and Foulger³¹ in which they administered large daily doses of thyroid extract to four normal individuals and observed an increase in the amplitude of the T-wave.

What is the peculiar nature of the pathological condition in the myxedema heart in order that it may give rise to the various phenomena

observed in the electrocardiogram? That the auricles as well as the ventricles can be involved is evident by the changes that can occur in the behavior of the P-wave. The fact that all chambers of the heart are dilated also speaks decidedly in favor of a generalized disturbance. No doubt the morbid process is a fairly well disseminated one. However, experimental work on thyroidectomized sheep and goats shows that arteriosclerosis, as well as cardiac dilatation with a flabby condition of the myocardium, frequently accompanies the myxedematous state (Goldberg³²). Many cases of myxedema are accompanied by disease of the coronary arteries, as was pointed out by Fishberg,³³ who found considerable arteriosclerosis in his cases post mortem. The frequency of arteriosclerosis may be explained by the fact that most of the patients with myxedema heart have already reached the age when arterial disease is common. The fact, however, that most of the graphic records assume their normal contour after thyroid treatment suggests that the disturbance in the conductive mechanism is essentially a physiological one, rather than permanent damage resulting from a coexisting coronary disease. Should coronary disease superimpose itself on a myxedema heart or vice versa, it is very questionable whether the graphic record would ever return to its normal form after thyroid therapy.

Autopsy evidence concerning the pathological condition of myxedema heart is very meager. It is possible to conceive a myxedematous infiltration being present in the heart muscle as well as in the skin and other tissues. Recent autopsy evidence indicates that something of such a nature actually occurs. Of the four cases of myxedema heart that came to autopsy at the Massachusetts General Hospital, three showed edema of the heart muscle with fibrosis; the fourth showed interstitial edema. On the basis of this evidence, it is not at all difficult to understand the rapid and striking changes seen in the graphic records following the administration of thyroid extract. The nature of the myxedematous fluid has been studied by Boothby and his associates.³⁴ They have shown that myxedematous patients when given thyroxin excrete in the urine a certain amount of nitrogen and that the nitrogen thus lost bears at the same time a relation to the weight loss. They conclude that the apparent edema which gave rise to the term myxedema is due to the disposition in the interstitial tissues of fluid containing about 2 per cent of nitrogen as protein. It is thus apparent that thyroxin mobilizes the myxedematous fluid and perhaps by some physico-chemical mechanism removes it gradually from the heart muscle. Furthermore, recent experimental evidence shows that thyroxin acts directly on the heart muscle and by doing so increases the amplitude and strength of the heart beat.^{34, 35, 36} It is probable, then, through the operations of these combined mechanisms, that the normal electrical potential differences of the conductive apparatus are slowly reestab-

lished. However, another important mechanism which is set up indirectly by the action of the thyroid extract comes into play. A myxedema heart is a generally enlarged flabby structure contracting sluggishly in the face of a diminished metabolism and oxygen deficiency. It is obvious that a myocardial anoxemia resulting from a diminished blood flow is present. This factor alone may be sufficient in itself to give rise to changes in the auricular and ventricular complexes. Following the inauguration of thyroid treatment, the minute output of the heart increases. This in turn augments coronary flow (Anrep and Segall³⁸) and thus restores a more adequate oxygen supply to the oxygen-deficient myocardium. That such a mechanism may operate very soon after the beginning of thyroid therapy could well explain the early changes which occur in the graphic records of the above two cases.

On this same basis it is possible to explain the danger of promiscuous thyroid treatment in myxedema heart where coronary narrowing from arteriosclerosis is suspected. Because the great increase in minute volume and blood velocity associated with the elevation of the basal metabolic rate involves a corresponding increase in the amount of work done by the heart, the oxygen requirement of the heart muscle is increased. This demand is normally met by an increase of blood supply consequent upon increased coronary flow. When the volume of coronary flow is reduced, because of coronary narrowing and failure of the coronary vessels to dilate, serious damage to the heart muscle may ensue. This may at times terminate in coronary occlusion with fatal myocardial infarction.³ Moreover, in cases of myxedema with concomitant hypertension, a drop in diastolic pressure usually occurs following thyroid medication. As a result coronary flow would be decreased and thrombosis formation facilitated.

DYNAMIC CONSIDERATIONS IN MYXEDEMA HEART

In discussing the dynamic events of myxedema heart, it is interesting to compare this type with the circulatory changes that occur in the hyperthyroid heart. Just as hyperthyroidism may cause marked myocardial overactivity, myxedema may on the other hand, produce retarded and sluggish underactivity of the heart muscle. Whereas in hyperthyroidism the prominent signs are tachycardia and loud, vigorous heart sounds, in myxedema, the outstanding signs are bradycardia and faint, feeble heart tones. It has been shown that the velocity of blood flow is reduced in myxedema heart and considerably increased in hyperthyroid heart (Blumgaard, Gargill and Gilligan²³). Concomitant with a reduced circulatory flow in myxedema there exists a reduced blood volume (Thompson⁴⁰). These probably are a result of depressed metabolic activities. Again, in hyperthyroidism, minute output^{23, 40, 41} is augmented while in myxedema it is reduced. A 20

per cent reduction in minute volume occurred in Case 2. It may also be added that in myxedema there is a diminished venous return to the heart as a result of the reduction in the strength of voluntary muscle contraction (Rockwell⁴³). In hyperthyroidism venous return is increased.

With this evidence in mind, speculations on the probable mechanism of cardiac dilatation and heart failure in myxedema can be made. It is recognized that a reduced blood volume and diminished circulatory rate with a slow pulse can explain a diminished cardiac output. It may be said that the circulatory load upon the heart in myxedema is actually diminished. These facts cannot in themselves explain the generalized dilatation of the heart which is found in at least 65 per cent of the cases. Then why should the myxedema heart become inefficient? This can best be explained on the ground that the inherent contractility of the myxedema heart is impaired or that the heart succumbs to a state of diminished tonus. In other words, the myxedema heart becomes in all respects a hypodynamic one.^{44*} In spite of the decreased load, it becomes weakened to the extent that, in order to do the same amount of mechanical work, it must dilate. To accomplish this, the muscle fibers must lengthen (Starling, and Visscher⁴⁵). Thus the dilatation is a compensatory mechanism on the part of the myocardium in an attempt to maintain normal minute volume. However, when the myxedematous heart dilates to a point beyond which it is no longer able to maintain normal minute volume, systolic discharge is decreased and venous pressure will, in consequence, rise. At this stage the mechanical efficiency of the heart is seriously impaired. We then have the onset of true heart failure. If we accept the idea that the pathological change in myxedema heart is generalized throughout the entire myocardium—a fact which is verified by x-ray and electrocardiographic evidence—then it is not difficult to conceive why all chambers of the heart should become weakened simultaneously. Thus the right heart does not have to wait for the left heart to fail. Hence, the factors which operate to impose right heart failure are facilitated in myxedema heart. Fortunately, were it not for the fact that this mechanism is counterbalanced—at least in the early stages of the disease—by a coexisting lowered blood volume and diminished venous return, it is probable that the incidence of gross congestive failure would be higher.

We can thus summarize the outstanding differences between the hyperthyroid heart and myxedema heart. In the former, because of the direct action of an excess of thyroxin in the heart muscle, the cardiac tone is increased as indicated by increased vigor and loudness of heart sounds with a corresponding increase in heart rate. As a

*The "hypodynamic state" is a term applied by Wiggers⁴⁴ to indicate a condition of the heart muscle in which, in spite of increasing venous pressure, systolic discharge is reduced and dilatation of the heart occurs.

rule, there is an increase in systolic pressure. The result is an increased velocity of circulation and an augmented minute volume. However, we cannot consider the hyperthyroid heart as a true hyperdynamic heart (one in which there is increased tonus), because it is possible that the minute volume increase is consequent upon the tachycardia rather than upon the ventricular tonus. On the other hand, the myxedema heart is characterized by a diffuse dilatation of all chambers and by a slow and feeble contraction as indicated by the faint heart sounds. There is eventually a reduction in minute volume accompanied by a diminished velocity of blood flow. The blood pressure as a rule is slightly elevated. This heart is fundamentally hypodynamic in that the working capacity or tonus of the ventricles is reduced, resulting in such a disproportion between diastolic volume and intraventricular pressure increase that for a given pressure rise, there is a much greater increase in volume.

COMMENT

The wide variation in the incidence of congestive failure associated with myxedema as reported by various authors is at the present time impossible to explain. It does not appear to be a matter of improper diagnosis because the concept of gross failure with its objective signs is not only well and uniformly accepted but likewise easily recognized. True enough, the beginning signs of myocardial weakness may be masked to a certain extent by the myxedematous state or the myxedematous condition may in some way interfere with the gross manifestations of an early congestive failure when it would otherwise be apparent. It is also probable that when gross congestive failure appears, it indicates that venous congestion has already progressed to a moderate extent. Other factors that may possibly retard or accentuate the appearance of gross failure are the level of the basal metabolic rate, the degree of secondary anemia, the blood volume, the extent of physical activity participated in by the patient, and the coexistence of coronary disease or hypertension.

When does the true inception of heart failure in myxedema supervene, and what should constitute the criteria by which one can judge the onset of myocardial insufficiency? It is certain that increased venous pressure and decreased minute output with a dilated heart can exist before signs of gross failure in myxedema are evident. Case 2 is a good example of such a situation. It was mentioned previously that this patient's chief complaint was dyspnea. Dyspnea appears to be an outstanding symptom in myxedema. Thus in the series from the Massachusetts General Hospital²⁰ as previously mentioned, 65 per cent showed dyspnea while only 3 per cent showed gross congestive failure. When a diffusely dilated heart, accompanied by signs of dyspnea, can be demonstrated, then we probably have the existence of early cardiac

failure. This condition was proved to be present in Case 2 when minute volume determinations showed a decreased systolic discharge. Fahr³ is probably correct when he states that in cases of myxedema which show definite cardiac dilatation, the onset of the condition of heart failure is present. When gross congestive signs will appear, of course, cannot be predicted, but eventually they will manifest themselves. Of the 65 per cent of cases of myxedema which showed definitely dilated hearts, it is very likely that they are the same 65 per cent which showed dyspnea. It would not be surprising, as further studies should show, that a direct correlation will be found to exist in regard to the degree of dilatation, dyspnea and minute output.

It is recognized that conclusions cannot be drawn from the study of this single case. Nevertheless, the suggestion is offered that if more cases are studied from the same angle, much will be learned concerning the problem of heart failure in myxedema.

SUMMARY

The literature on myxedema heart is reviewed and two additional cases are reported. The myxedema heart is unique in the respect that it returns to its normal size after the administration of adequate amounts of thyroid. Upon the withdrawal of thyroid it again dilates and characteristic changes in the electrocardiogram occur. The pathologic physiology of myxedema heart is discussed. Minute volume studies carried out in the case in which dyspnea was the outstanding symptom suggest that myocardial insufficiency may be present even when the gross objective signs of congestive failure are absent. It is assumed, therefore, that when a generalized cardiac dilatation, accompanied by dyspnea, can be demonstrated, congestive heart in myxedema is in all probability present.

REFERENCES

1. Zondek, H.: Das Myxö-demherz, München. med. Wehnschr. 65: 1180, 1918.
2. Lerman, J., Clark, R. J., and Means, J. N.: The Heart in Myxedema, Ann. Int. Med. 6: 10, 1933.
3. Fahr, G.: Myxedema Heart, AM. HEART J. 8: 1, 1932.
4. Assman, H.: Das Myxö-demherz, München. med. Wehnschr. 66: 9, 1919.
5. Meissner, R.: Zur Klinik des Myxö-demherzen, München. med. Wehnschr. 67: 1316, 1920.
6. Laubry, C., Mussio-Fournier, and Walser, J.: Syndrome Angineux et Insuffisance Thyroïdienne, Bull. et mém. Soc. méd. d. hôp. de Paris 48: 1592, 1924.
7. Fahr, G.: Myxedema Heart, J. A. M. A. 84: 345, 1925.
8. Curschman, H.: Ueber Myxödema der Erwachsenen, Med. Klin. 22: 559, 1926.
9. Duden, Chas.: Myxedema With Cardiac Decompensation and Hypertension Which Disappeared Under Thyroid Medication, J. Missouri M. A. 26: 25, 1929.
10. Davis, Jay C.: Myxedema Heart, Ann. Int. Med. 4: 733, 1931.
11. Barron, M.: Personal communication.
12. Zins, Berthold, and Rösler, H.: Kasuistischer Beitrag zur Beeinflussung des Myxödemenherzens durch Thyroidin, Wien. klin. Wehnschr. 39: 1353, 1926.
13. Schittenhelm, A., and Eisler, B.: Ueber die Wirksamkeit des Thyroxins beim Endokrin Bedingten Störungen, Klin. Wehnschr. 6: 41, 1926.

14. Holzman, J. E.: Myxedema Heart, *AM. HEART J.* 4: 351, 1929.
15. Christian, H. A.: 'The Heart and Its Management in Myxedema, Rhode Island M. J. 8: 109, 1925.
16. Willius, F., and Haines, S.: Status of Heart in Myxedema, *AM. HEART J.* 1: 67, 1925.
17. Means, J., White, P., and Krantz, C.: Observations on the Heart in Myxedema, *Boston M. & S. J.* 195: 455, 1926.
18. Case, C. E.: An Analysis of Fifty-Eight Cases of Myxedema, *Clifton M. Bull.* 11: 112, 1925.
19. Ayman, D., Rosenblum, H., Falcon-Lesses, Mark: "Myxedema Heart" Without Evidence of Cardiac Insufficiency, *J. A. M. A.* 98: 20, 1932.
20. Means, J. H.: Hypothyroid Heart Disease, *New England J. Med.* 208: 10, 1933.
21. Tung, C. L.: Status of the Heart in Myxedema, *AM. HEART J.* 6: 734, 1931.
22. Wiggers, Carl: Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease, *J. A. M. A.* 96: 8, 1931.
23. Blumgaard, H. L., Gargill, S. L., and Gilligan, D. R.: Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, *J. Clin. Investigation* 9: 91, 1930.
24. Leug, W.: Ueber das Electrocardiogram des Myxödems, *Ztschr. f. klin. Med.* 104: 337, 1926.
25. Nobel, E., Rosenblüth, A., and Samet, B.: Das Electrocardiogram des kindlichen Myxödems, *Ztschr. f. exper. Med.* 43: 332, 1924.
26. White, P. D.: Quoted in reference 17.
27. Reid, W. D., and Kenway, F. L.: Electrocardiographic Signs Associated With Low Basal Metabolism, *Endocrinology* 13: 191, 1929.
28. Thacher, C., and White, P.: Electrocardiogram in Myxedema, *Am. J. M. Sc.* 171: 61, 1926.
29. Ziskin, T.: Angina Pectoris Associated With Myxedema Heart, *U. S. Vet. Bur. Med. Bull.* 4: 24, 1930.
30. Gardner, E.: *Lancet* 44: 10, 1924.
31. McGuire, J., and Foulger, M.: Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiograph With Special Reference to the T-waves, *AM. HEART J.* 8: 114, 1932.
32. Goldberg, S.: Changes in Organs of Thyroidectomized Sheep and Goats, *Quart. J. Exper. Physiol.* 17: 15, 1927.
33. Fishberg, A.: Arteriosclerosis in Thyroid Deficiency, *J. A. M. A.* 82: 463, 1924.
34. Boothby, W. M., and Sandiford, I.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects. 1. A Method of Studying the Reserve or Deposit Protein, With a Preliminary Report of the Results Obtained, *Ergebn. d. Physiol.* 24: 728, 1925.
35. Yater, W. M.: The Tachycardia, Time Factor, Survival Period and Seat of Action of Thyroxin in the Perfused Hearts of Thyroxinized Rabbits, *Am. J. Physiol.* 98: 338, 1931; Mechanism of Adjustment of the Circulation in Hyperthyroidism, *AM. HEART J.* 8: 1, 1932.
36. Andrus, E. C.: Heart in Hyperthyroidism: A Clinical and Experimental Study, *AM. HEART J.* 8: 1, 1932.
37. Kurt, Felix: *Proc. Staff Meetings Mayo Clinic* 4: 285, 1929.
38. Anrep and Segall: Regulation of Coronary Circulation, *Heart* 13: 239, 1926.
39. Anrep, G. V., Davis, J. C., and Volhard, E.: Effect of Pulse Pressure Upon Coronary Flow, *J. Physiol.* 73: 405, 1931.
40. Thompson, W. O.: The Blood Volume in Myxedema, With a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, *J. Clin. Investigation* 2: 477, 1926.
41. Blalock, A., and Harrison, T. R.: The Effects of Thyroidectomy and Thyroid Feeding on the Cardiac Output, *Surg. Gynec. & Obst.* 44: 617, 1929.
42. Burwell, C. S., Smith, W. C., and Neighbors, D. W.: The Output of the Heart in Thyrotoxicosis, *Am. J. M. Sc.* 178: 157, 1929.
43. Rockwell, J. G.: Personal communication.
44. Wiggers, C. J.: Circulation in Health and Disease, Philadelphia, 1923, Lea & Febiger.
45. Starling, E. H., and Visscher, M. B.: Regulation of Energy Output of Heart, *J. Physiol.* 62: 3, 1927.

STUDIES IN OSCILLOMETRY*

ALFRED FRIEDLANDER, M.D.

CINCINNATI, OHIO

OSCILLOMETRY has been in use as a diagnostic method for over fifty years. Recently, however, the French school under the leadership of Vaquez, Gomez, and others, has awakened renewed interest in this subject. Their emphasis has been placed very largely on the height of the oscillometric curve on the one hand, and the recognition of the so-called mean blood pressure on the other.

The method of approach in the studies of which this communication forms a preliminary report, was somewhat different. It concerned itself chiefly with the form of the oscillogram, readings being taken on all extremities in each instance.

METHOD

The Boulitte modification of the Pachon oscillometer has been used for all determinations.

This apparatus has two overlapping, distensible pouches having a combined width of fifteen centimeters. These pouches are enclosed in a rigid web cover fitted with web straps. The apparatus is strapped to the extremity to be studied. By a simple valve arrangement the pouches can be inflated together, or singly.

A manometric dial permits the recording of oscillometric variations at different pressures.

In each case studied, eight oscillograms are made, i.e., of the forearms, upper arms, legs, and thighs on both sides. With the band snugly fitted to the extremity, air is pumped in until the pressure is great enough (in ordinary cases) to prevent any movement of the oscillatory needle. In certain cases even at the pressure of three hundred millimeters of mercury (the limit of the instrument) oscillations still occur. By means of a needle valve, the pressure is dropped ten millimeters at a time, and the height of the oscillation recorded at the various pressures.

Inasmuch as the time element is a factor, the observer announces the oscillations at the various pressure levels, which are then immediately charted by an assistant. By the use of various chart symbols for the different extremities, the four oscillograms for the upper, and again for the lower extremities can be charted on one graph and the two graphs combined on one sheet. ∴

Blood pressure readings are taken by the auscultatory method on the right and left arms as soon as the arm oscillograms are charted. The patient lies recumbent during the test so that the extremities are approximately at the heart level.

Using this technic, several hundred charts were made of patients suffering from diverse conditions, using material from the medical service of the Cincinnati General Hospital.

*From the Department of Internal Medicine, College of Medicine, University of Cincinnati and the Vascular Disease Clinic, Cincinnati General Hospital.

OBSERVATIONS

It has become apparent that the height of the oscillometric curve is not greatly influenced by age or sex, provided that the heart is normal and the blood vessels not seriously involved. In all the cases studied, records were made of the physical findings, laboratory findings, electrocardiograms, teleroentgenograms, and other x-ray findings.

The oscillometric index is definitely labile in certain conditions where there is reason to believe that arteriospasm exists. Repeated readings on

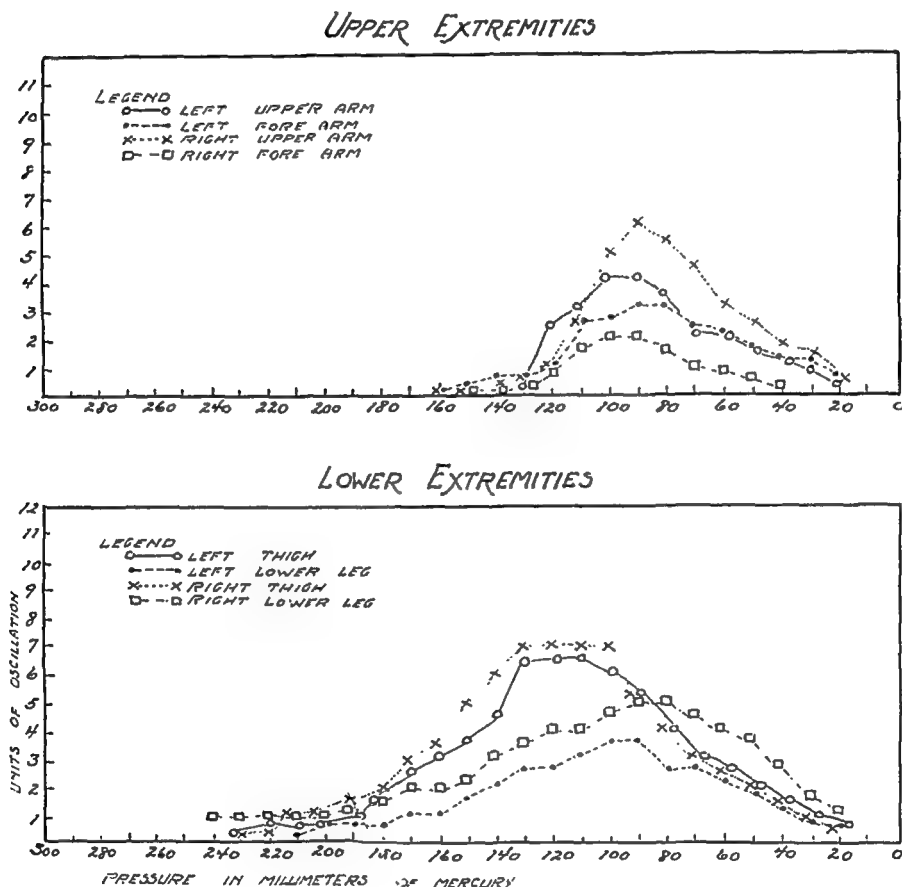


Fig. 1.—Normal oscillogram.

O. P., male, white, aged sixty-five years. Blood pressure 120/60. *Clinical diagnosis:* Pernicious anemia.

the same patient under such conditions will show varying heights of the oscillometric curve.

Experience also demonstrated that the maximal oscillometric phase (MOP) of the brachial oscillogram occurred between 100 and 80 mm. Hg in a great variety of cases, with apparently normal hearts and blood vessels. These findings are in accord with those of Miller and Chester.¹

The particular point to be emphasized in this preliminary report, is that in oscillometric studies, the form of the oscillogram is of paramount importance.

It would appear that from the type of oscillogram obtained, one may draw certain conclusions as to the condition of the vascular tree in a given case.

Four illustrative oscillograms are presented.

1. The normal oscillogram (Fig. 1) of the upper arm begins to show an oscillometric rise at about 120 mm. Hg and drops to zero between 40 and 30 mm. Hg. Oscillations do occur at higher pressures than 120 mm., but are not marked. The MOP occurs between 100 and 80 mm. Hg.

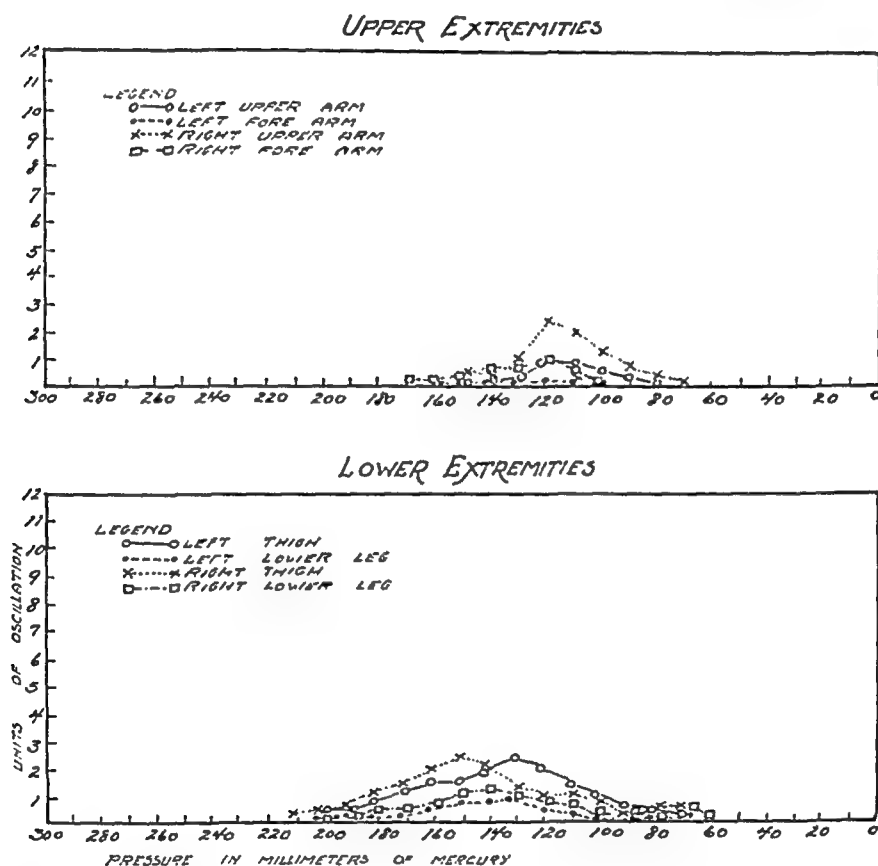


Fig. 2.—Generalized vascular sclerosis.

R. S., male, white, aged forty-nine years. Blood pressure 120/100. Clinical diagnosis: Arteriosclerotic heart disease and vascular sclerosis.

The thigh shows oscillations at higher pressures (around 160 mm. Hg), and the drop occurs around 40 mm.

The maximal oscillometric phase shows variations in unit height of oscillations varying from 5 to 6 units on the upper extremity, and up to 7 or 8 units on the thigh.

No conclusion can be drawn from the height of the oscillation as to the actual blood pressure.

2. The oscillogram in marked vascular sclerosis shows a very different picture (Fig. 2).

The oscillations occur over a much narrower range of pressure; the MOP, especially in the lower extremity, is apt to occur at higher pressures—140 to 120 mm. Hg, and the height of oscillation is low, 2 to 3 units.

3. Essential Hypertension.—Here the oscillogram presents a distinct variant from the normal.

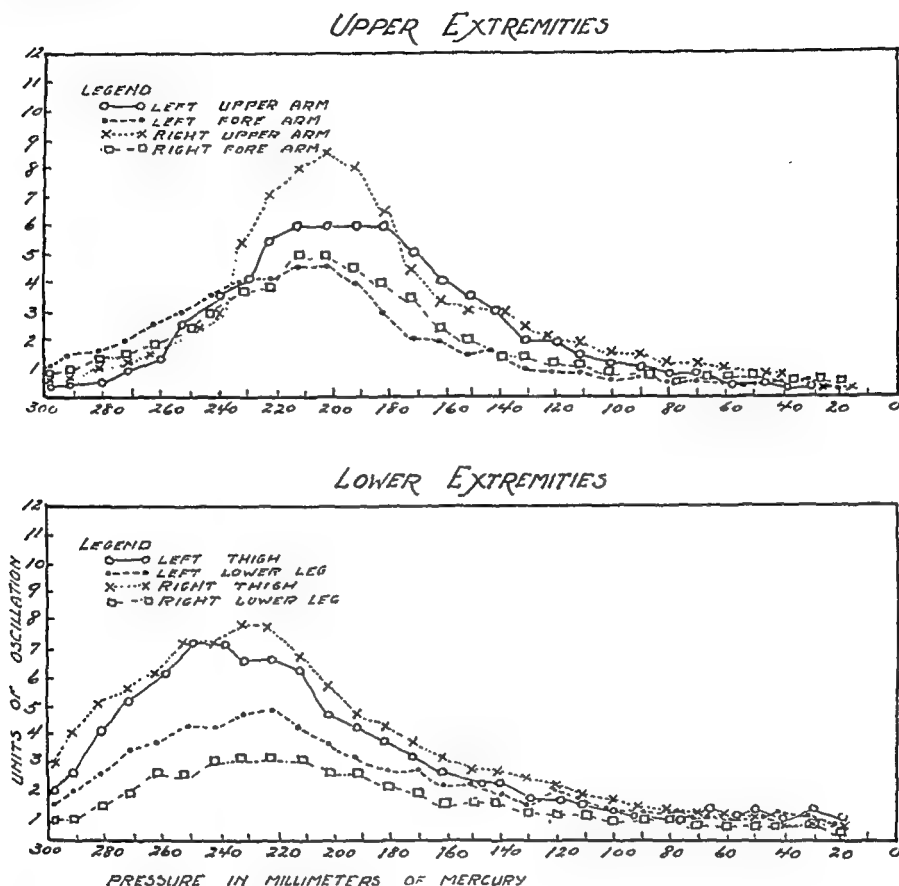


Fig. 3.—Essential hypertension.

E. T., female, white, aged fifty years. Blood pressure 250/160. Clinical diagnosis: Essential hypertension and nephrosclerosis.

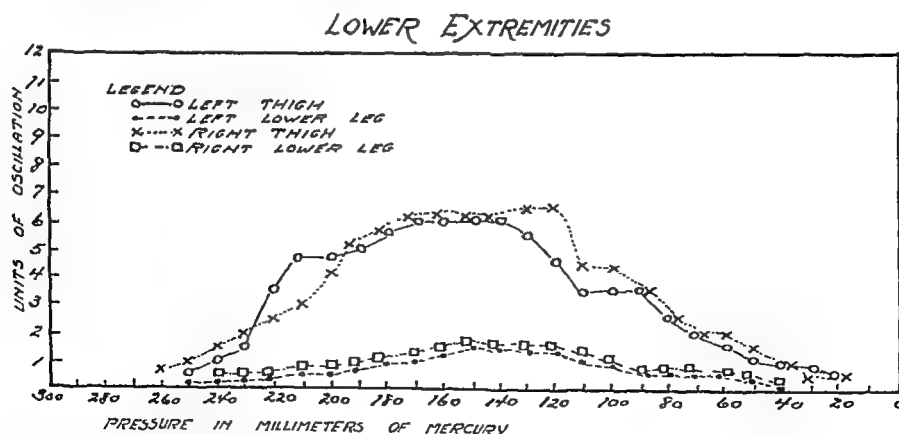


Fig. 4.—Medial arteriosclerosis.

L. L., female, white, aged sixty-eight years. Blood pressure 190/120. Clinical diagnosis: Arteriosclerosis. Marked in arteries of lower legs.

There is what might be called a definite shift to the left. In both upper and lower extremities, the MOP occurs at much higher levels (220 to 200 mm. Hg). Oscillations begin at such high pressures as 300 mm. Hg. Thus, as will be noted in Fig. 3; oscillations stood at 3 units at 300 mm. Hg in the right thigh. Furthermore the oscillations approach zero at much higher pressures (around 100 mm. Hg). The unit height of the oscillations is high, 8 to 9, at the MOP.

4. Medial arteriosclerosis (Fig. 4). The striking features of the oscillogram here are, first, the marked difference in the curves of the legs and thighs; second, there is the wide spread of the oscillations beginning around 240 mm. Hg and extending to 40 mm. Hg. The MOP occurs at high level and is often, as in the case illustrated, of the plateau type (170 to 120 mm. Hg).

COMMENT

Too much emphasis must not be laid upon the mere height of the oscillometric curve. In the absence of cardiac hypertrophy and vascular sclerosis, the MOP may show a wide degree of variation in diverse conditions. It even shows great variations in the same patient at different times, depending upon conditions of vasoconstriction, etc. This is well demonstrated in cases of hyperthyroidism without involvement of heart or blood vessels. Allisat² also calls attention to this fact.

Oscillograms must be interpreted on the basis of the factors which maintain blood pressure, i.e., the force of the cardiac contraction (the *vis a tergo*), the condition of the blood vessel wall, and the very important factor of peripheral resistance. Whether the fourth factor, blood volume and blood viscosity, is of great importance or not, cannot be decided so definitely at this time.

Samuels³ in referring to the value of the oscillogram in the study of circulation in the extremities, calls attention to the help given by the oscillogram in differentiating neurogenic from organic arterial disease.

Kramer⁴ says that the oscillogram gives information about the deeper vessels which cannot be palpated. It may suggest the occurrence of collateral circulation when definite lesions of the blood vessels are apparent.

Vaquez and his coworkers⁵ have stressed the importance of the so-called "mean pressure," as determined by the oscillogram. They conclude that, very often, hypertension is disclosed by elevation of the mean pressure at an earlier age than is shown by elevation of the systolic blood pressure. They apparently pay no attention to the form of the oscillogram.

As one surveys the rather extensive literature on oscillography which has appeared recently, one is struck by the fact that in nearly all studies, the main emphasis has been placed on the maximal oscillographic phase (MOP). It is the purpose of this communication to call attention to the

much greater importance of the oscillogram itself. From the form of the oscillogram, certain definite deductions may be drawn as to the condition of the vascular tree.

Three typical pathological oscillograms are shown herewith, to demonstrate diverse conditions. It should be added that these types of tracings have been found over and over again, in the several hundred cases studied. The tracings run true to form, so to speak, and it is quite possible to predicate the type of vascular lesion present from the oscillogram itself.

It must, of course, be added that mixed forms occur, as would be expected from the general nature of vascular sclerosis. In such cases definite diagnosis cannot be made from the oscillograms alone.

1. Where the oscillograms of both extremities (upper and lower) are of the low flat type, with oscillations occurring within a comparatively narrow range and with the MOP relatively low (2 to 3 units), there is true arterial thickening, with or without calcification. This condition is well illustrated in Fig. 2. This patient was a white male, aged forty-nine years, with the typical clinical picture of arteriosclerotic heart disease with general vascular sclerosis.

2. The curve in true arterial hypertension without major arterial involvement is characterized by a definite shift to the left. That is, the MOP occurs at high pressure levels, and is itself high. This is well illustrated in Fig. 3, where the MOP occurs at 230 mm. Hg in the lower extremities, and 200 mm. Hg in the upper, with an index of 7 and 8 units respectively. This patient was a white female, aged fifty years, with the clinical picture of hypertension and nephrosclerosis.

3. The curve in hypertensive heart disease with senile arteriosclerosis (Mönckeberg type) is characterized by high thigh curves and low leg curves, or by high curves of one lower extremity and low curves of the other.

In his original communication Mönckeberg⁶ in discussing his so-called medial calcification, stressed the fact that medial calcification is much commoner in the extremities than arteriosclerosis. Karsner⁷ says that the early change is usually a fatty degeneration of the middle layers of the musculature and elastica of the media, which may be associated with necrosis. The condition is common in old age and affects particularly such arteries as the femoral, radial, temporal, and dorsalis pedis. Severe degrees of peripheral senile sclerosis may be associated with but little sclerosis of the aorta.

Beck⁸ reviewed oscillometric curves taken at various levels in cases of thrombo-angiitis obliterans, as well as in cases of peripheral thrombosis and embolism, and compared these readings with those at corresponding levels in the unaffected limb. He found that the oscillometric index at the point just proximal to the point of occlusion, was definitely and consistently larger than the index at the same level in the unaffected limb.

This did not hold good when the lesion was sclerotic in character. In the series of cases studied by the author, this type of curve was found very frequently. The curve shown in Fig. 4, was taken from a white woman aged sixty-eight years with distinct hypertensive heart disease and marked peripheral sclerosis.

SUMMARY

1. The form of the oscillogram, taking curves of all extremities in each case, is of more importance than the estimation of the maximal oscillometric phase.

2. The normal oscillogram may show definite variations in the MOP in the same individual at different times. This is dependent largely upon the condition of peripheral resistance.

3. Typical pathological oscillograms are shown, demonstrating arterial thickening, essential hypertension with nephrosclerosis, and hypertensive heart disease with Mönckeberg arteriosclerosis.

4. From the form of the oscillogram in typical cases definite conclusions may be drawn as to the condition of the vascular tree.

5. Mixed forms of curve are often found. In such cases the oscillogram alone cannot afford definitive diagnosis as to the condition of the vessel walls.

It affords me pleasure to acknowledge a debt of gratitude to Dr. L. G. Herrmann for much constructive criticism and many valuable suggestions given during the course of these studies.

REFERENCES

1. Miller, H. R., and Chester, W.: *AM. HEART J.* 8: 389, 1933.
2. Allisat, E.: *Ztschr. f. klin. Med.* 122: 436, 1932.
3. Samuels, S. S.: *J. A. M. A.* 88: 1780, 1927.
4. Kramer, D. W.: *Am. J. M. Sc.* 185: 402, 1933.
5. Vaquez, H., Gley, P., and Gomez, D. M.: *Presse méd.* 39: 281, 1931.
6. Mönckeberg, J. G.: *Virchow's Archiv.* 171: 141, 1903.
7. Karsner, H. T.: *Human Pathology*, Philadelphia, 1926, Lippincott, p. 463.
8. Beck, W. C.: *J. A. M. A.* 99: 842, 1932.

THE USE OF QUINIDINE IN AMBULATORY PATIENTS FOR
THE PREVENTION OF PAROXYSMS OF AURICULAR
FLUTTER AND FIBRILLATION; WITH ESPECIAL
REFERENCE TO DOSAGE AND THE EFFECTS
ON INTRAVENTRICULAR CONDUCTION*

HARRY GOLD, M.D., HAROLD L. OTTO, M.D.,
AND HARRY SATCHWELL, M.D.
NEW YORK, N. Y.

DETAILED studies on the use of quinidine in auricular flutter and fibrillation have been conducted mainly in cases of the "persistent" forms of these rhythms or during a prolonged attack with the patient at rest and under close supervision. They show that the drug may be relied upon in the majority of suitable cases to abolish auricular flutter or fibrillation and to reestablish a normal rhythm for varying periods of time and with a fair degree of safety. The prevention of attacks in the paroxysmal form of auricular flutter and fibrillation, however, presents somewhat different problems from the practical standpoint, and these may account for the fact that, in general, not quite the same success has been attained in this, as in the treatment during a paroxysm. During the past two years we have followed the clinical course in some detail in twenty-one patients with paroxysmal auricular fibrillation or flutter. These included two cases of active rheumatic carditis, one case of hyperthyroidism, eight cases of arteriosclerosis, two cases presenting no evidence of organic heart disease (Class E), and the remaining ones with heart disease of unknown origin. In several of those who received quinidine in varying doses—in some up to 50 grains daily—the attacks remained uninfluenced; while in a few in whom the attacks appeared to have been diminished in frequency or abolished at one time or another, the influence of the drug could only occasionally be definitely established.

It was a common observation that a dose of quinidine which seemed at one time to render a patient free of attacks, appeared at another time to be without this protective action. This observation, however, may signify any one of a number of different phenomena, such as spontaneous variations in the course of the disease, the development of tolerance to the drug, or extraneous reflexes that may render a circus movement more or less resistant. Under the ordinary conditions of life the patient is subject to widely varying influences—rest, effort, excitement, shock, digestive disorders—all of which are sources of

*From the Department of Pharmacology of Cornell University Medical College and the Cardiac Clinics of the Beth Israel Hospital and the Hospital for Joint Diseases.

metabolic changes or reflex stimuli that may in susceptible individuals serve to start or abolish a circus movement in the auricle. The plan of putting such a patient to bed, establishing the dosage which appears to abolish the attack under these conditions, and then prescribing such doses for long periods of time does not afford an adequate solution of the problem, for the reason that such doses will frequently fail to prevent the recurrence of attacks.

Most of these patients are ambulatory. They may or may not present evidence of organic heart disease. In any case they often complain of little more than these attacks of palpitation and other symptoms such as dyspnea, faintness and weakness attending a paroxysm. Some are entirely without abnormal symptoms during a paroxysm, the presence of the abnormal rhythm being discovered during one of the routine examinations. The incidence, the duration, and the intensity of attacks are likely to vary widely at different times and in different individuals, adding further uncertainties in attempting to assess the usefulness of the drug and to establish suitable dosage for the prevention of attacks.

Among the obstacles in the way of systematic investigation and treatment of these cases with drugs, should be mentioned the lack of continued cooperation on the part of the patient. It is a matter of no difficulty to excite a patient's enthusiasm for a course of quinidine therapy just after a few severe paroxysms that have occurred in a period of a week or two, but it is difficult to sustain his cooperation in the continued daily use of large doses of quinidine for periods of many months in which he is free of attacks. There is a question, indeed, whether such treatment is desirable. The fact is, however, that the use of the drug is interrupted and the attacks recur.

It may be noted that while the control of the paroxysmal forms of auricular flutter and fibrillation presents greater difficulties, the use of quinidine in these cases, has, from one point of view, the advantage of greater safety, even though these patients cannot be subjected to the same degree of supervision as the ones confined to bed. In the paroxysmal forms quinidine may be given in the presence of a normal rhythm to prevent attacks, the only danger being the direct toxic effects of the drug, while in the treatment with quinidine during an attack there are the additional dangers of the very rapid tachycardias in the intermediary stages between the abnormal and the normal rhythm as well as the possibility of the discharge of emboli when the auricles begin to contract after fibrillation has persisted for some time.

One of our cases was extremely favorable for a systematic study; the paroxysms were relatively frequent, they were sufficiently intense to interfere with the patient's occupation, and the intervals between attacks, though very irregular, showed a range sufficiently restricted to afford a basis for comparison. This patient consulted us at the

clinic in August, 1930, because of severe attacks of palpitation during which he was completely incapacitated. They had occurred at frequent intervals during the preceding period of about four years, during which time he had received various forms of treatment but had not obtained any relief. After a considerable interval (before electrocardiograms could be obtained during a paroxysm in order to establish the diagnosis of paroxysmal auricular flutter and fibrillation) treatment with quinidine was started without any interruption of the patient's activities. The result is that, except for intervals during which the drug was withheld for purposes of study, the patient has been virtually free of distressing symptoms for a period which up to the time of writing is about two years.

The observations in this case present several features of special interest with regard to the use of quinidine, more particularly (1) the prolonged administration of extremely large doses of quinidine, (2) the use of quinidine in the presence of intraventricular block, and (3) the almost complete relief of subjective symptoms by a mechanism of quinidine action that does not diminish the frequency but does reduce the intensity of the paroxysms. We report this study in detail together with special observations carried out in ten other patients, bearing on quinidine dosage, the effect of quinidine on intraventricular conduction and the danger of vagal pressure in the presence of a tachycardia.

CASE REPORT

History.—Patient J. B., forty-four years of age, was born in Russia, was married, had three children, and reported good habits. His previous medical and surgical history was negative. He did not smoke. He took tea and coffee in moderation, and no alcohol. He discovered he had heart trouble in 1926 (about six years ago) when he began to be aware of undue shortness of breath and fatigue on effort. About a year later he became subject to attacks of palpitation associated with faintness and weakness. He stated that during these periods the heart "pounded" rapidly and sometimes irregularly. He was usually compelled to interrupt his work during the attacks, although in the intervals he was not seriously troubled with cardiac symptoms and he had no difficulty in continuing with his regular occupation as a tailor. The attacks sometimes appeared while the patient was at rest, although in most instances they seemed to have been brought on by sudden exertion, excitement, fright, eating, or a cold drink. The onset was usually abrupt, the duration variable, and the termination usually abrupt. He had consulted several physicians and had been treated at clinics. For nearly a year up to the time of admission, he had been taking 20 drops of a tincture of digitalis three times daily. From time to time he had received various other medicines including quinidine in small doses. The intensity and severity of the attacks, however, remained uninfluenced.

Physical Examination.—The patient was a healthy looking white male weighing 150 pounds. The significant physical findings were as follows: The heart rate ranged between 60 and 80 per minute and was regular except for occasional ventricular premature beats; the sounds at the base were very distant, and the first sound at the apex was replaced by a systolic murmur not transmitted in any direction; there were no diastolic murmurs. There were no thrills. The left auricle and

ventricle were found considerably enlarged on fluoroscopic examination. The blood count was normal and the blood Wassermann reaction negative. The blood pressure ranged from 118 to 140 systolic, 65 to 90 diastolic. There were no signs of peripheral arteriosclerosis (eye grounds and other peripheral arteries) or peripheral congestion. The electrocardiogram showed a regular sinus rhythm with a bundle-branch block (Fig. 2).

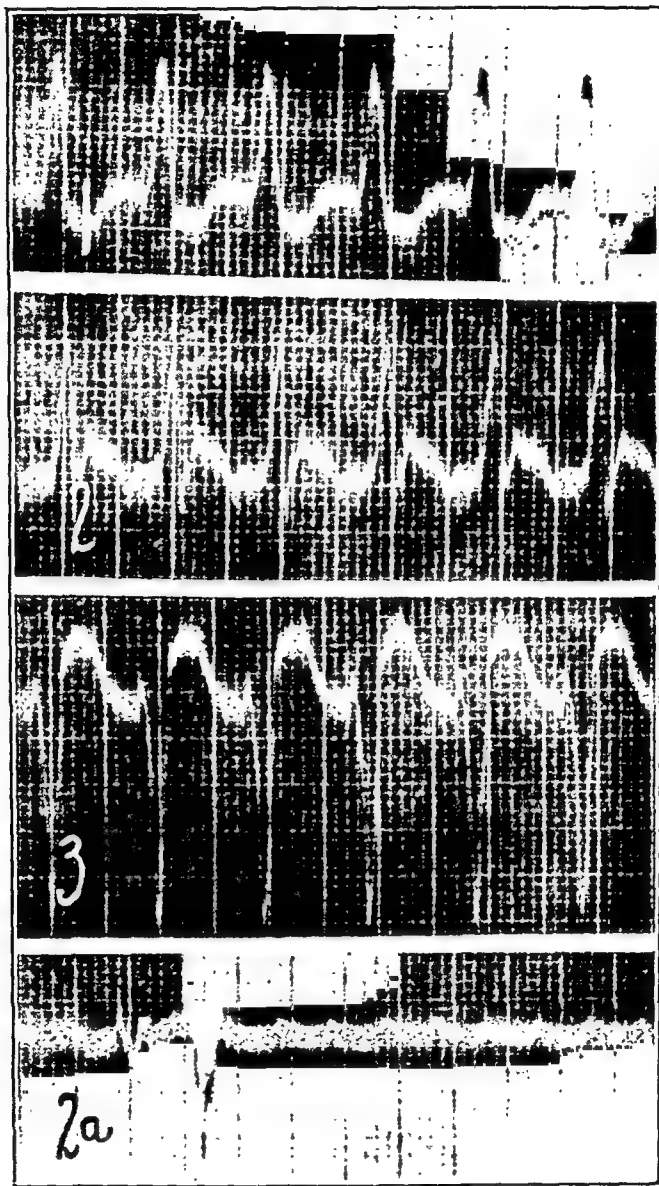


Fig. 1.—Tracing of patient J. B. taken 10/15/30. Auricular flutter with bundle-branch block. Tracing 2 a shows ventricular arrest with flutter waves of the auricle during "vagal" pressure.

The diagnosis was heart disease of unknown origin, enlarged heart, normal sinus rhythm, bundle-branch block and slight diminution of functional capacity (Class IIA*). Subsequently there was added to this paroxysmal auricular flutter and fibrillation (Fig. 1).

*Following the nomenclature adopted by the Heart Committee of the New York Tuberculosis and Health Association.

It may be noted that it was about two months after admission to the clinic before an electrocardiogram was obtained during an attack. At this time the heart rate was 150 per minute and regular. Carotid pressure caused complete heart-block with ventricular arrest during which the auricular flutter at 300 per minute could be counted. About three weeks later the patient was again seen during an attack during which the heart rate was also 150 per minute and the rhythm very irregular. Carotid pressure was now without any influence. The tracing taken at this time showed auricular fibrillation.

Incidence and Character of Attacks Before Quinidine.—In some cases of paroxysmal auricular fibrillation and flutter, the attacks are occasionally so mild as to escape the patient's notice, and in these it is difficult to obtain a reliable record of attacks as a basis for a study. As we have already indicated, however, the attacks

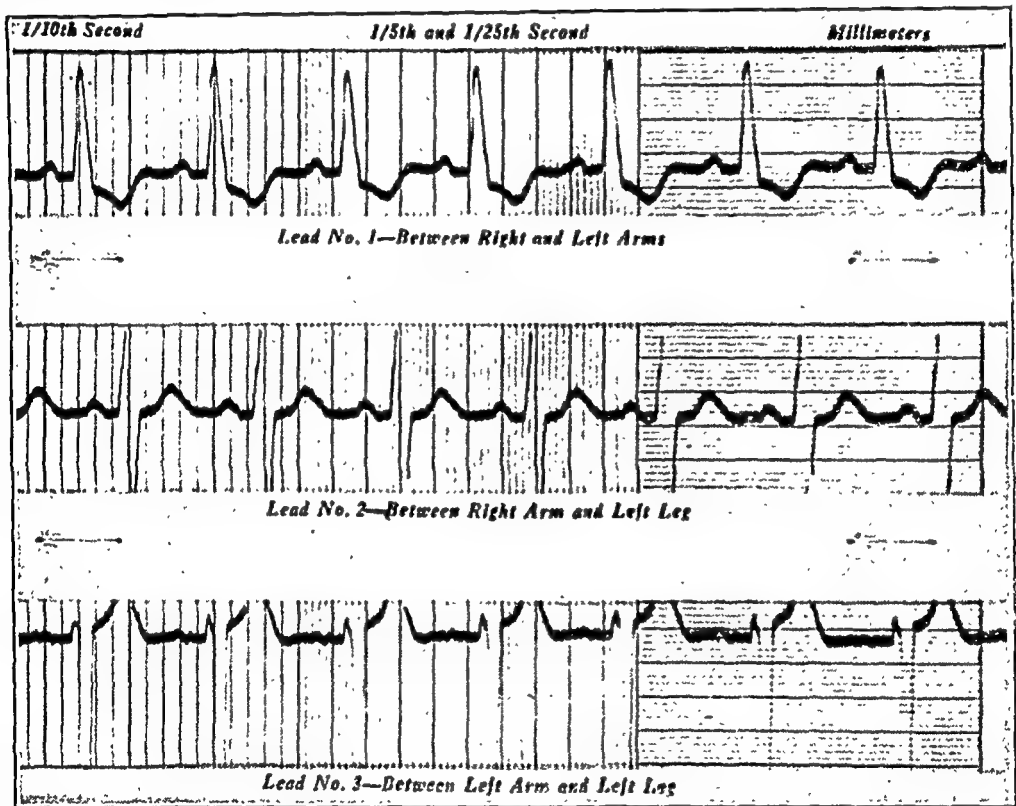


Fig. 2.—Tracing of patient J. B. taken 8/18/30 before quinidine was given. The P-R interval is 0.20 and the QRS time is 0.12 second.

of palpitation in this patient were very distressing and interfered seriously with his occupation. These factors helped to insure the patient's complete cooperation in any effort that offered the possibility of relief. Before he came under our observation, he had been instructed by a physician to keep a record of the incidence and duration of attacks as well as of suggestive factors that seemed to him to incite them. This record he brought to us, and together with that made during the control period in our clinic, constitutes a fairly accurate account of the paroxysms during a period of about thirty-one months. These are presented in Table I. An examination of this table shows that before adequate treatment the patient had had 37 attacks of auricular flutter or fibrillation in a period of about thirty-one months. The attacks varied in duration from about one to sixty hours and appeared at intervals varying from five to sixty-six days. At one time there were as many as 3 attacks in a month and at another time two months passed without an attack.

During this entire period of more than two and one-half years, therefore, the patient suffered on the average of one attack in about twenty-five days, lasting on the average about thirteen hours.

TABLE I
INCIDENCE OF ATTACKS BEFORE TREATMENT WITH QUINIDINE IN PATIENT J. B.

DATE	DURATION OF ATTACKS IN HOURS	INTERVALS BETWEEN ATTACKS IN DAYS
4/28/28	48	--
6/ 4/28	13	37
6/28/28	2.5	24
7/12/28	1.5	14
7/19/28	1.5	7
9/ 1/28	3	44
10/10/28	12	39
10/22/28	3	12
12/27/28	3	66
2/14/29	2.5	49
3/31/29	9	45
5/ 1/29	7.5	31
5/21/29	60	21
7/ 6/29	1	46
8/24/29	6	49
9/27/29	16.5	34
10/10/29	6.5	13
11/ 6/29	13	27
12/18/29	8	42
1/ 9/30	3	22
1/18/30	2	9
1/23/30	17.5	5
1/29/30	18	6
3/29/30	12	59
4/ 7/30	4	9
4/16/30	5	9
5/12/30	3	26
5/26/30	12	14
6/ 3/30	24	8
6/30/30	4	27
7/14/30	15	14
8/ 5/30	50	22
8/28/30	23	23
9/25/30	30	28
10/15/30	23	20
10/30/30	15	15
11/21/30	17	22

Incidence and Character of Attacks During Treatment With Quinidine.—A similar record was obtained during the period of treatment with quinidine. The facts are tabulated in Table II, which includes in addition the results of all the clinical examinations of the heart and analyses of the electrocardiograms.

Treatment was started with a daily dose of 12 grains of quinidine sulphate (6 grains twice daily) which was continued over a total period of twenty-eight days. During this time the patient had two severe attacks similar to the previous ones.

The dose was increased to 30 grains daily (10 grains three times daily) and in a period of six days there were 4 attacks of palpitation. This was the first time that the attacks had ever occurred with such frequency. It was, however, also the first time that the attacks were so "mild," producing only a slight sense of irregular palpitation during which the patient continued his work without serious discomfort.

The dose was increased to 40 grains daily (10 grains every four hours). In this period there was an almost continuous attack of mild palpitation which hardly disturbed the patient at all, and which lasted during the seven days in which this dose was taken and during the succeeding seven days in which a dose of 50 grains daily (10 grains every three hours) was taken. This attack was not absolutely continuous, but the interruptions in the abnormal rhythm in this period of two weeks were of very brief duration. The electrocardiograms taken during these attacks which the patient described as almost negligible showed auricular fibrillation with relatively slow ventricular rates of from 70 to 92 per minute as compared with the rate of 150 per minute seen before the quinidine.

The dose was then increased to 60 grains daily (10 grains every two hours) and during the total period of twenty-eight days in which this dose was taken there were four attacks which were again so mild as to be practically negligible in the mind of the patient. At times the sense of palpitation and irregular heart action was so slight as to make it difficult for him to be certain as to the time of onset and disappearance of the attacks.

Maximum Tolerance.—Inasmuch as attacks still occurred at this level, the dosage was increased to 70 grains daily and during the next two weeks there were no attacks, although the period is too short to ascertain whether attacks were possible at this level of dosage. There appeared, however, some blurring of vision and impaired hearing, and after two weeks these doses were discontinued. This procedure showed, therefore, that at one period at least, in this patient, the doses of quinidine which failed to prevent attacks of paroxysmal flutter or fibrillation completely were very near to the largest doses that could be tolerated without extra-cardial toxic symptoms.

Prolonged Effects.—In the subsequent course, as seen in Table II, an attempt was made to ascertain whether some lasting effect might not result from the prolonged treatment with quinidine in such a case, so that smaller doses would maintain the status established by the large ones. During this test only two paroxysms occurred in a total period of 213 days after daily doses varying from 20 to 50 grains. This is considerably longer than the longest intervals between attacks before the use of quinidine. However, since this status could not be maintained subsequently by similar doses, the significance of this observation remains uncertain. That there is some lasting effect after prolonged treatment was shown during the period of the larger doses. A dose of 60 grains daily was taken continuously, up to the time of writing, for 364 days. This appeared to be the optimum daily dosage in this patient, because at this level of dosage the paroxysms were milder and less frequent than with the smaller doses. The continued use of this dosage has given a much longer period (nearly one year) of freedom from paroxysms than at any time during the control.

As already indicated, during the early period of about fifteen months in which the larger doses of quinidine were used, the patient regarded himself as almost "cured." There was not a single attack sufficiently severe to make it necessary for him to discontinue his work, although this was necessary during practically every attack before the quinidine therapy. The attacks which now occurred were so mild and disturbed the patient so little that their frequency was for a time lost sight of and the impression gained hold in the clinic that this was a patient whom quinidine had rendered almost free of paroxysms of auricular flutter and fibrillation. We were, therefore, surprised to discover upon careful analysis of the data that not only was the patient not rendered free of attacks during that period, but that on the contrary, their frequency had actually increased. Leaving out of consideration the almost continuous attack lasting two weeks during the early stages

TABLE II

INCIDENCE OF ATTACKS DURING TREATMENT WITH QUINIDINE IN PATIENT J. B.

DATE	DAILY DOSE OF QUINIDINE IN GR.	TOTAL CONTINUOUS PERIOD OF GIVEN DOSE IN DAYS	DURATION AND SEVERITY OF ATTACKS IN HOURS	INTERVAL BETWEEN ATTACKS IN DAYS	RHYTHM	RATE	P-R	QRS
8/11/30	0	--	--	--	NSR, VPC	60	--	--
8/18/30	0	--	--	--	NSR, VPC	80	0.20	0.12
8/25/30	0	--	--	--	NSR, VPC	72	--	--
8/28/30	0	--	23, severe	23	--	--	--	--
9/ 8/30	0	--	--	--	NSR, VPC	68	--	--
9/25/30	0	--	30, severe	28	--	--	--	--
9/29/30	0	--	--	--	NSR, VPC	92	--	--
10/15/30	0	--	23, severe	20	A. Flutter	A300 V150	--	0.12
10/20/30	0	--	--	--	NSR, VPC	65	--	--
10/30/30	0	--	15, severe	15	A. Flutter	A300 V150	--	--
11/ 3/30	0	--	--	--	NSR, VPC	76	--	--
11/21/30	0	--	17, severe	22	A. Fibrill.	150	--	0.12
11/24/30	0	--	--	--	NSR, VPC	64	--	--
12/ 8/30	12	14	--	--	NSR, VPC	64	--	--
12/17/30	12	23	12, severe	26	--	--	--	--
12/20/30	12	26	49, severe	3	A. Fibrill.	130	--	0.12
12/22/30	12	28	--	--	NSR, VPC	78	--	--
12/25/30	30	2	7, mild	3	--	--	--	--
12/27/30	30	4	12, mild	2	--	--	--	--
12/28/30	30	5	7, mild	1	--	--	--	--
12/29/30	30	6	5+, mild	1	A. Fibrill.	90	--	0.15
12/30/30	40	1	12+, mild	1	--	--	--	--
1/ 5/31	40	7	almost constant	--	A. Fibrill.	88	--	0.15
1/12/31	50	7	almost constant	--	A. Fibrill.	92	--	0.17
1/19/31	50	14	mild	6	A. Fibrill.	70	--	0.17
1/21/31	60	2	brief, mild	2	--	--	--	--
1/22/31	60	3	brief, mild	1	--	--	--	--
1/26/31	60	7	--	--	NSR	70	0.24	0.16
1/29/31	60	10	15 min., mild	7	--	--	--	--
2/ 2/31	60	14	--	--	NSR	64	--	--
2/ 6/31	60	18	10, mild	8	NSR	60	--	--
2/16/31	60	28	--	--	NSR	60	0.24	0.14
3/ 2/31	70	14	--	--	NSR	56	--	--
3/ 4/31	0	2	18, mild	26	--	--	--	--
3/ 7/31	0	5	18, mild	3	--	--	--	--
3/ 9/31	0	7	--	--	NSR	60	--	--
3/23/31	50	14	--	--	NSR	62	--	--
4/ 6/31	50	28	--	--	NSR	60	0.23	0.13
4/15/31	40	9	brief, mild	39	--	--	--	--
4/17/31	40	11	brief, mild	2	--	--	--	--
4/20/31	40	14	--	--	NSR	63	--	--
5/ 4/31	50	14	--	--	NSR	72	--	--
5/18/31	50	28	--	--	NSR	72	--	--
6/15/31	50	56	--	--	NSR	70	--	--
7/13/31	40	28	--	--	NSR	60	0.20	0.13
8/ 1/31	20	19	18, severe	106	--	--	--	--
8/10/31	20	29	--	--	NSR	70	0.20	0.12
9/28/31	30	49	--	--	NSR	60	--	--

TABLE II—CONT'D

DATE	DAILY DOSE OF QUINIDINE IN GR.	TOTAL CONTINUOUS PERIOD OF GIVEN DOSE IN DAYS	DURATION AND SEVERITY OF ATTACKS IN HOURS	INTERVAL BETWEEN ATTACKS IN DAYS	RHYTHM	RATE	P-R	QRS
10/19/31	20	21	--	--	NSR	60	--	--
11/ 2/31	20	35	--	--	NSR	70	0.20	0.12
11/16/31	10	14	5, mild	107	NSR	80	0.20	0.12
12/ 1/31	20	15	24, severe	15	--	--	--	--
12/ 7/31	20	21	8, mild	6	--	--	--	--
12/14/31	20	28	--	--	NSR	68	--	--
12/28/31	30	14	6, 15, 3½, mild	3 in 2 wk.	NSR	70	0.20	0.12
1/11/32	40	14	mild, brief	14?	NSR	64	--	--
1/22/32	50	11	brief, mild	11?	--	--	--	--
1/25/32	50	14	--	--	NSR	68	--	--
1/29/32	50	18	brief, mild	7?	--	--	--	--
2/15/32	50	35	--	--	NSR	70	0.20	0.13
2/29/32	60	14	brief, mild	3 in 2 wk.	NSR	60	--	--
3/28/32	60	42	brief, mild	--	NSR	68	--	--
4/11/32	60	56	--	--	NSR	65	0.24	0.15
5/ 2/32	60	77	--	--	NSR	60	0.24	0.16
5/16/32	60	91	--	--	NSR	60	0.24	0.16
5/23/32	60	98	--	--	NSR	60	0.24	0.16
6/ 6/32	60	112	--	--	NSR	60	0.18	0.15
6/27/32	60	133	--	--	NSR	60	0.24	0.16
7/18/32	60	154	--	--	NSR	70	0.24	0.16
8/29/32	60	196	--	--	NSR	60	0.24	0.15
9/26/32	60	224	--	--	NSR	62	--	--
10/24/32	60	252	--	--	NSR	60	0.24	0.16
12/19/32	60	308	--	--	NSR	64	0.24	0.16
2/13/33	60*	364	--	--	NSR	60	0.24	0.16

NSR (Normal sinus rhythm) ; VPC (ventricular premature contractions).

*A daily dose of 70 grains was taken for one week during this period to determine the development of tolerance to quinidine.

(?) Indicates that the exact interval could not be established in these cases.

of the quinidine therapy, there occurred at least 30 attacks in about fifteen months, or, on the average, at least one attack in about fifteen days in this period, as compared with one in about twenty-five days during the time before the quinidine therapy, and such frequency as five attacks in one week had never been approached in the entire control period of over two and a half years.

An examination of the clinical records and the electrocardiograms taken during the period of quinidine therapy shows that starting at the level of 30 grains daily, ventricular premature contractions disappeared. During the period of auricular fibrillation there was in evidence, at this level of dosage, depression of both A-V conduction and intraventricular conduction, the ventricular rate having slowed from one of 150 to about 90 per minute, and the QRS time having increased from 0.12 to 0.15;* the maximum QRS time of 0.17 second appeared at the level of dosage of 50 grains.

*The figures for P-R and QRS intervals represent the average of ten readings in every instance.

The normal sinus rate was not slowed by any doses of quinidine, although there was a tendency to moderate bradycardia during the control period. During the periods of normal sinus rhythm, A-V conduction was found impaired only during the level of dosage of 50 to 60 grains, the normal P-R interval of 0.20 second increasing to 0.24 second. Simultaneously intraventricular conduction was usually impaired, the QRS time increasing from 0.12 to 0.16 second.

DISCUSSION

Mechanism of Action.—In the foregoing case the use of large doses of quinidine resulted in marked relief of symptoms. There were two different mechanisms, however, by which this was obtained. While after prolonged treatment paroxysms appeared to have been completely abolished, in the first period of about one year almost complete relief of subjective symptoms was obtained at a time when contrary to expectations the frequency of paroxysms had not diminished but markedly increased.

In the presence of auricular fibrillation quinidine frequently at first accelerates the ventricular rate owing to depression of the vagi.¹ Quinidine may, however, depress A-V conduction by a direct action of the drug upon the conduction tissues.¹ Usually this latter action does not play an important rôle in the therapeutic effects of the drug in auricular flutter or fibrillation. In this case, however, the beneficial effects of quinidine for about fifteen months were expressed almost entirely by this action on A-V conduction. Whereas the ventricular rate ranged around 150 during the attacks of fibrillation before the quinidine therapy, they now ranged around 80 to 90 per minute. The maximum effect on the ventricular rate resulted from a daily dose of quinidine which increased the P-R interval during the normal sinus rhythm by 0.04 second, although marked interference with passage of impulses from the fibrillating auricles to the ventricles occurred during a much lower level of dosage (30 grains daily) which was insufficient in this patient to produce any change in the P-R interval during the normal sinus rhythm.

Before ascribing the greater frequency of the paroxysms to a direct action of quinidine, it was necessary to take into consideration the fact that as the patient improves he is very likely (though he denied it) to permit himself more frequent exposure to influences that provoke attacks, such as excitement and indiscretion in diet. This did not appear to play any part in this case because, as seen in Table II, 5 attacks occurred in the first week in which the larger doses were used. The greater frequency of the attacks appears, therefore, to be due to a direct action of the drug, and while quinidine usually renders the auricles unfavorable for fibrillation or flutter, in this case during one period the opposite occurred.

Lewis and his coworkers¹ showed that quinidine may exert two antagonistic effects in the auricle, lengthening the refractory time which

would tend to abolish the circus movement, and slowing of the speed of conduction which would tend to prevent its cessation. A relative preponderance of this latter action in our patient would explain the observation in the early period of the quinidine therapy that paroxysms of fibrillation occurred more frequently and that one attack persisted almost continuously for two weeks, although not one paroxysm in a period of more than four years had ever lasted as long as three days. With the larger doses of 60 grains daily, however, sufficient increase in the refractory time probably occurred to render the auricle

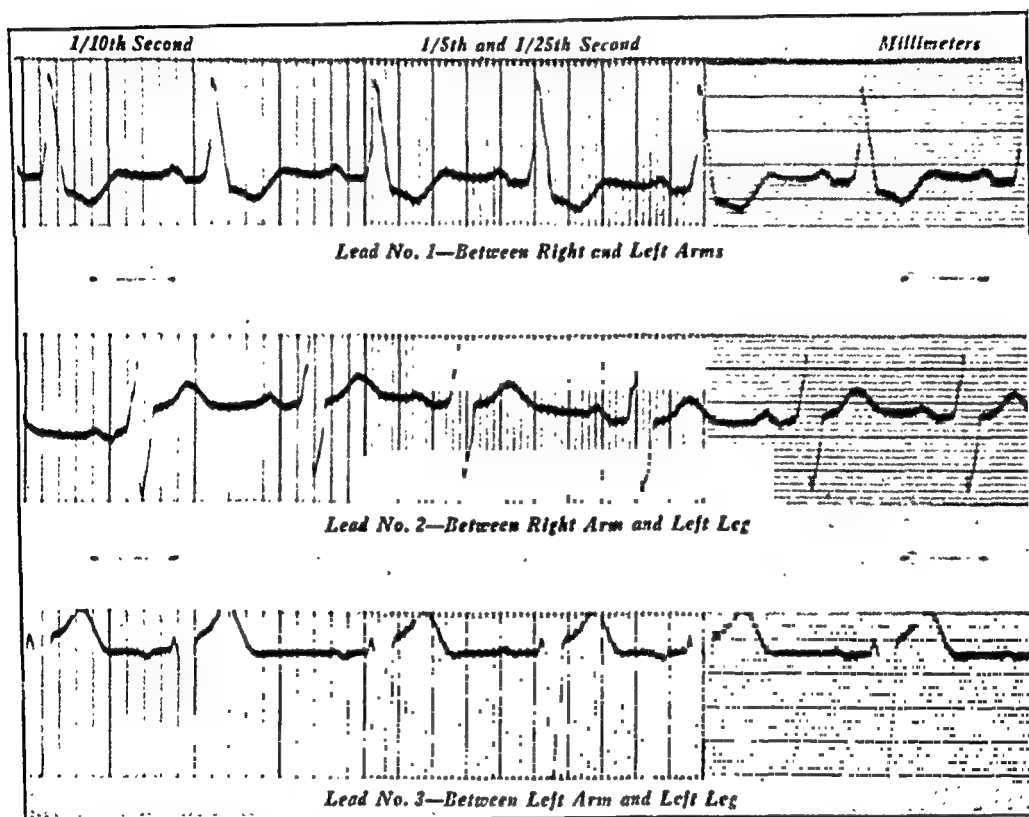


Fig. 3.—Tracing of patient J. B. taken 8/29/32 after a daily dose of 60 grains of quinidine sulphate for a period of twenty-eight weeks. The P-R interval is 0.24 second and the QRS time is approximately 0.16 second.

less favorable for fibrillation or flutter because during this level of dosage, the attacks were of very brief duration and subsequently completely disappeared.

Quinidine in the Presence of Bundle-Branch Block.—Quinidine depresses intraventricular conduction,² and under some conditions bundle-branch block believed to be due to quinidine has been reported.^{3, 4} Wilson and Wishardt⁵ reported a case of fatal poisoning with quinidine in which the electrocardiogram showed progressive spreading of the QRS group until the normal contour of the ventricular deflections was lost. The presence of bundle-branch block in our case presented, therefore, a theoretical contraindication to the use of large doses of quinidine. However, doses up to 30 grains daily dur-

ing the period of normal sinus rhythm produced no change in the QRS time, while doses of 60 grains produced a prolongation of the intraventricular conduction time by about 30 per cent (Fig. 3). With a fixed dosage, this effect was not progressive and promptly disappeared when the dose was diminished. Viko, Marvin and White⁴ did not observe any prolongation of the QRS time during quinidine therapy (dosage not stated) in 3 patients who had bundle-branch block at the start. We administered quinidine to 8 patients with normal sinus rhythm, whose tracings showed a normal QRS time, and found that daily doses of 30 grains increased the QRS time by 33 per cent in one case, and daily doses of 50 grains increased the QRS time by 20 per cent in another case. It may be fairly assumed, therefore, that in the presence of bundle-branch block intraventricular conduction does not necessarily show any unusual susceptibility to depression by quinidine. It would be well, however, in view of the possibility of producing serious impairment of intraventricular conduction with large doses of quinidine, in any case, even in the presence of a normal QRS time, to control the gradual increase in dosage, as in this patient, by frequent electrocardiograms.

Vagal Pressure.—We have already referred to the influence of vagal pressure in this patient during an attack of flutter. Vagal pressure has been used in experimental studies^{6, 7} and is commonly employed for various diagnostic purposes, especially for differentiating types of tachycardias. It is well known that in auricular flutter vagal pressure frequently causes the ventricular rate momentarily to diminish to one-half by the production of a greater degree of A-V block. Such an effect helps to distinguish this from auricular paroxysmal tachycardia, in which the same procedure may cause complete disappearance of the ectopic rhythm. In cases in which pressure over the carotid sheath fails, other procedures such as a deep inspiration or pressure on the eyeballs will frequently produce a similar change in the ventricular rate. The diagnosis is sometimes uncertain without this test. For example, in the case of patient J. B., it was only in the period of ventricular arrest produced by vagal pressure that the deflections of auricular flutter could be seen (Fig. 1). During the vagal pressure lasting 16 seconds, however, alarming symptoms occurred; there was a sensation of heat, followed by marked pallor and almost complete loss of consciousness. In the presence of a fatigued A-V conduction, the vagal pressure caused complete block lasting 16.4 seconds, with ventricular arrest during the first 5.5 seconds, and only 7 escaped idioventricular beats appeared during the entire period of 16.4 seconds. This was followed by a prolonged period of auricular flutter with an irregular ventricular response. Fairly long periods of cardiac arrest following vagal pressure have been reported by others.

Nathanson⁸ recently described a case in which cardiac standstill for a period of 7.2 seconds occurred in an old patient with a sinus rhythm after right vagal pressure. Although in our experience, as well as in that of others, vagal pressure has proved to be a relatively safe procedure, it needs hardly to be mentioned that such sudden and marked fluctuations in heart rate as occurred in our patient, from 150 to 30 per minute, are to be avoided.

From time to time, attention has also been called to alarming symptoms that occasionally appear as a result of vagal pressure.⁷ This was

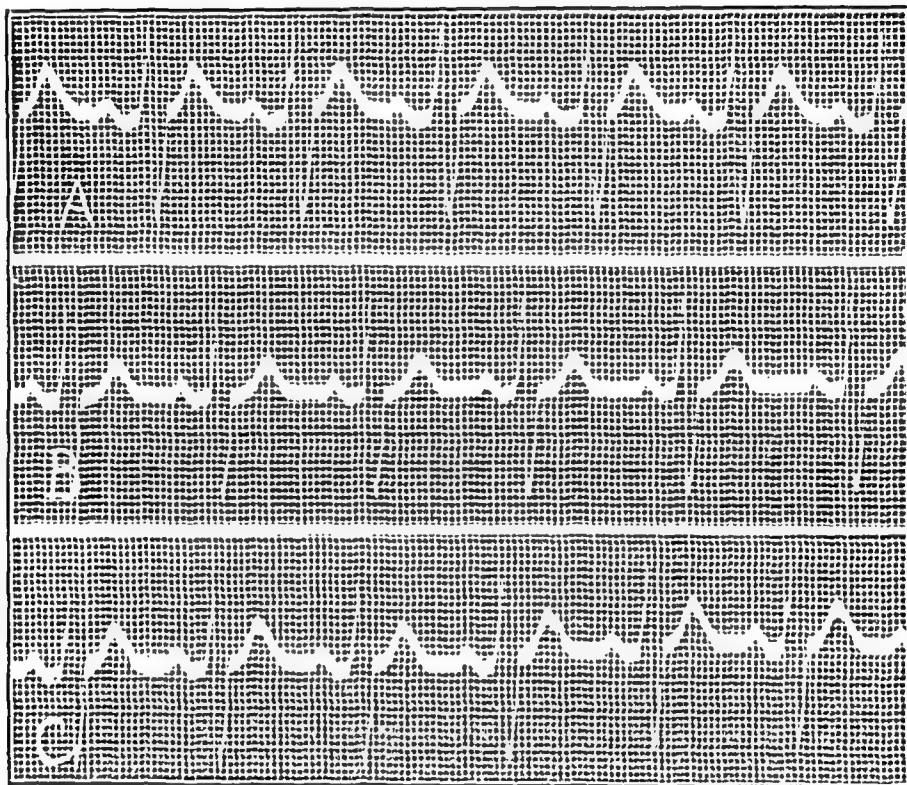


Fig. 4.—Tracings of patient J. B., Lead II only, showing the rapid recovery from the effects of quinidine. A, Taken 5/24/32, after 60 grains quinidine sulphate daily for ninety-nine days, shows P-R interval of 0.250 second and QRS time of 0.164 second; B, taken 5/25/32, after quinidine was withheld for twenty-four hours, shows P-R interval of 0.220 second and QRS time of 0.139 second; C, taken 5/26/32, after 60 grains quinidine sulphate in twenty-four hours, shows P-R interval of 0.230 second and QRS time of 0.158 second.

shown by another case of auricular flutter which came to our attention* and in which additional observations also illustrate in a striking manner the effect of a tachycardia on ventricular automaticity.

This patient, a male, aged sixty-two years, had arteriosclerotic heart disease and a moderate degree of functional limitation. His blood pressure was 130/70 mm. He was admitted to the hospital during an attack of auricular flutter in which the electrocardiogram showed an auricular rate of 320 and the ventricular beat was practically regular at a rate of 150 per minute. On some days the ventricular beat was found to be irregular and slow due to flutter with varying A-V block. Right

*This patient was seen by one of us (H. G.) on the Second (Cornell) Medical Division of Bellevue Hospital through the courtesy of Dr. Ephraim Shorr.

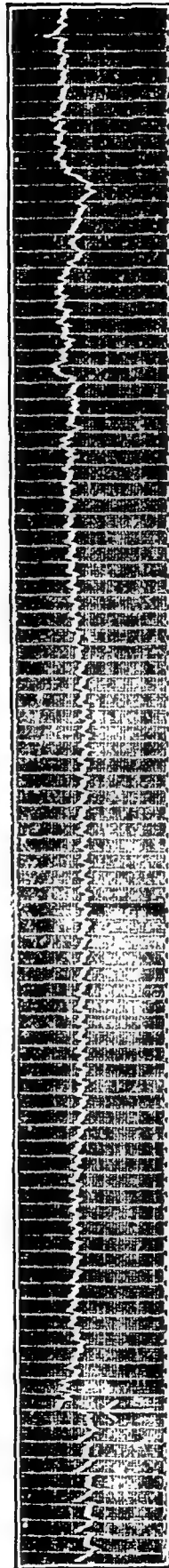


Fig. 5.—Tracing of patient with auricular flutter in whom "vagal" pressure produced ventricular arrest for 15.4 seconds resulting in a convulsion. The arrow indicates the point at which "vagal" pressure was applied.

vagal pressure was applied several times during the course of this attack. In each case the vagal pressure resulted in ventricular arrest, and the pressure was continued until ventricular action was resumed or alarming symptoms appeared. At one time (May 23, 1932) when the ventricular rate was slow (80 per minute) due to flutter with irregular block, vagal pressure resulted in complete ventricular arrest for only 6.8 seconds. At another time (May 20, 1932) when the ventricular rate was rapid (150 per minute), vagal pressure resulted in complete ventricular arrest for much longer periods of time—9.8 seconds (in the test performed in the morning), and 15.4 seconds (in the test performed in the afternoon). The latter pause resulted in a convulsion. The long duration of this period of ventricular standstill as the result of vagal pressure is unusual. The tracing is reproduced in Fig. 5.

We have stressed the danger of vagal pressure in connection with these cases because rapid excitation of the ventricle (as by an auricular flutter) tends to depress its automaticity,^{9, 10} and, therefore, the production of complete heart-block by vagal pressure during a tachycardia is particularly liable to result in prolonged arrest of the ventricle. In the diagnostic use of this test it would diminish the risk by applying the vagal pressure only momentarily.

Dosage.—Although the average dose of quinidine in the treatment of auricular fibrillation is from about 15 to 30 grains daily, there are several reports on the use of extremely large doses. Viko, Marvin and White⁴ gave daily doses up to 60 grains. Levine and Fulton¹¹ gave as much as 112 grains in twenty-four hours to one patient with ventricular tachycardia, and 36 grains daily for months to another. In our patient the dosage was gradually increased to the point of minor toxic effects. Altogether he consumed a total of 38,456 grains (more than 75 ounces of quinidine sulphate) or an average of about 48 grains daily for 802 days. It is well to note, however, that a daily dose of quinidine probably exerts its maximum action in the first few days and that practically no appreciable cumulation, in terms of effects, is in evidence when this dose is continued for months. There are several experimental studies which show that quinidine is very rapidly excreted.^{12, 13} In the present case when 70 grains of quinidine were given daily, visual and auditory disturbances occurred after the first day, continued in about the same intensity during the two weeks, and disappeared the day following the withdrawal of the drug. The continued use of a daily dose of 60 grains over a period of one year did not show enough cumulation to give as marked effects as 70 grains daily given for one day.

Inasmuch as the development of tolerance to the drug during prolonged administration would vitiate the significance of the absence of subjective symptoms as an indication of the absence of cumulation, the dose was increased to 70 grains daily for one week, after 60 grains daily had been taken for almost one year. The results show that appreciable tolerance had apparently not developed because during this test ringing in the ears and mild deafness appeared, as it did during similar dosage in the early part of the study.

Interesting observations also bearing on this point were made in this patient using conduction changes as criteria of quinidine action (Fig. 4). After a daily dose of 60 grains for about three months, the tracing (tracing A) taken two hours after the last dose of 10 grains, showed a P-R interval of 0.250 second as against the control of 0.20 second, and a QRS time of 0.164 second as against 0.12 second in the control. Marked recovery was in evidence twenty-four hours after the drug was discontinued, the tracing then showing a P-R interval of 0.22 second and a QRS time of 0.139 second (tracing B). The drug was then administered for one day, and 60 grains (tracing again taken two hours after the last dose of 10 grains) produced almost the full effect upon the QRS time that was maintained by that daily dosage for months, namely, QRS time of 0.158 second (tracing C). The P-R interval after this dose was 0.233 second showing that in this case it required more than one daily dose to produce the full effect on A-V conduction. However, after a daily dose of 60 grains for one week, the P-R interval was found prolonged by about 20 per cent beyond the control and the QRS time by about 30 per cent, and the continued use of such dosage for about twelve months did not produce any greater effect.

One frequently finds in the literature that the doses of quinidine necessary to reestablish a normal rhythm are expressed in terms of total quantities.³ From the foregoing it is clear, however, that the fact of importance in the matter of dosage of quinidine, from the standpoint of the therapeutic effects,^{*} but more especially of toxic effects, is the *size of the daily dose rather than the length of time such doses are continued*, or the total quantity taken over a period of time, and that in the case of a dose which has not caused toxic effects in the first few days, it is unlikely that toxic cardiac effects from the direct action of the drug will result from its continued administration for long periods of time. It may be well to state that emphasis should be placed, in this connection, on the toxic *cardiac* effects, because, as has been shown by Gold and Modell,² the elimination of quinidine from cardiac structures is apparently faster than from other structures—for example, the central nervous system—so that repeated doses of quinidine which may give no indication of cumulation in the changes produced in the electrocardiogram, may, if large enough, show sufficient cumulation to produce toxic effects by action upon the central nervous system.

We have already referred to several factors which appear to influence the size of the daily dosage of quinidine in the ambulatory patient. A series of observations carried out in another patient are of importance in this connection and may be reviewed briefly.

^{*}Therapeutic effects are sometimes seen only after the repetition of a fixed daily dose for several days, but this is apparently due mainly to a changing susceptibility of the abnormal mechanism rather than to cumulation of the drug.

This patient, M. K., aged twenty-six years, had rheumatic heart disease with mitral insufficiency and enlarged heart. There was no impairment in functional capacity. During the past two years he had been subject to attacks of paroxysmal auricular fibrillation and flutter (rate of the flutter varying from 210 to 300 per minute). Because of the rheumatic infection his A-V conduction was frequently found prolonged, the tracing showing P-R intervals as high as 0.26 second and dropped beats. This probably accounted for the fact that the ventricular rates during the periods of fibrillation and flutter were only occasionally faster than 100 per minute. He was given quinidine and the dosage was gradually increased until he received 50 grains daily (10 grains at approximately three-hour intervals). Larger doses exceeded his tolerance and produced toxic symptoms (dizziness, mild deafness and ringing in the ears) so that it was not possible to ascertain whether they would prevent the paroxysms.

An effort was made to establish the single dose of quinidine which during auricular flutter would reestablish a sinus rhythm in this patient. During the visit to the clinic a tracing was taken, and when flutter was present a dose of 10 grains of quinidine sulphate was given by mouth. The patient then rested quietly and additional tracings were taken at hourly intervals. This dose sufficed to reestablish a sinus rhythm within one to two hours in four out of five such tests carried out during a period of six weeks. The effect appeared in approximately the time required for the production of the maximum effects of a dose of quinidine as observed by others.¹⁴ Yet in a period of sixteen months (including the above mentioned six weeks), auricular flutter prevailed when the patient appeared at the clinic during fourteen of seventeen visits, although he was taking 30 to 50 grains of quinidine sulphate daily, divided into capsules of 10 grains each at approximately four-hour intervals, the last dose being taken approximately two hours before the examination. A rest period in the clinic during five of these sessions, similar to that during the special tests, did not establish a normal rhythm.

This illustrates, therefore, that while during rest this patient was fairly susceptible to quinidine, so that a single dose of 10 grains sufficed to abolish flutter and reestablish a normal rhythm, under the ordinary conditions of activity he appeared so resistant that doses up to 50 grains daily were insufficient to keep him free of paroxysms.

It is common practice to prescribe small maintenance doses of quinidine (usually of the order of about 6 grains daily) to prevent relapse to fibrillation after a normal sinus rhythm has been established by large doses. There is as yet no sufficient proof that such a plan of dosage plays any material rôle in the persistence of the normal rhythm. Viko, Marvin and White⁴ found that relapses to fibrillation occurred in as many patients who received continued "maintenance" doses of quinidine as in those in whom quinidine was discontinued after the normal rhythm was established, although the dissimilarity between some aspects of the two groups led them to the view that the "maintenance" dose did exert some influence. Our own experience leads us to the belief that the routine use of the smaller maintenance doses of quinidine to prevent the recurrence of flutter or fibrillation in the ambulatory patient is probably not sound, and that in general more intense quinidine effects are necessary to overcome the influences in the ambulatory patient that tend to precipitate an at-

tack of fibrillation or flutter than those necessary to abolish an attack in the patient that is confined to bed. Indeed the necessary intensity of quinidine effects may even exceed the patient's tolerance for the drug so that it becomes impossible to prevent attacks while the patient is up and about, as in the case (patient M. K.) just cited. To what proportion of cases the foregoing observations are applicable remains to be determined by more intensive study of larger numbers of ambulatory patients with paroxysmal auricular fibrillation and flutter.

SUMMARY AND CONCLUSIONS

1. In the way in which quinidine has been employed up to the present time, it has not proved so useful for the prevention of paroxysmal attacks of auricular flutter and fibrillation in the ambulatory patient as for the abolition of such attacks in the patient confined to bed. Some of the reasons for this are discussed.

2. It is indicated that there is less danger in the use of quinidine in patients with paroxysmal auricular fibrillation and flutter to prevent attacks than to abolish the abnormal rhythm during a paroxysm.

3. Although quinidine depresses intraventricular conduction (prolongs QRS time) the presence of bundle-branch block due to heart disease does not indicate necessarily any undue susceptibility to this action of quinidine.

4. Illustrations are cited of the value and dangers of "vagal" pressure during a tachycardia. Because rapid excitation of the ventricle is liable to impair its automaticity, "vagal" pressure in auricular flutter may, by producing complete heart-block, cause prolonged arrest of the ventricle with alarming symptoms.

5. Depression of A-V conduction by quinidine usually does not play an important rôle in the therapeutic effects of the drug in auricular flutter and fibrillation. However, in one case which we report, depression of A-V conduction by very large doses of quinidine was solely responsible for the almost complete symptomatic relief during a period of more than a year. Another unusual aspect of the action of quinidine in this patient was the fact that the frequency of the paroxysms of fibrillation or flutter were not diminished but were nearly doubled during this period. The probable mechanism of this unusual reaction to quinidine is discussed.

6. A fixed daily dose of quinidine produces its full effects very early, so that if it has not produced toxic effects in the first few days, it is unlikely that toxic effects from the direct action of the drug will result from its continued administration for long periods of time. Thus in one of our patients a daily dose of 60 grains of quinidine sulphate prolonged the A-V conduction time by 20 per cent and the

intraventricular conduction time by 30 per cent after the first few days, but the continued use of this dose for 364 days did not increase these effects further.

7. Since quinidine is rapidly excreted and shows very slight "cumulation," the matter of importance in dosage is the size of the daily dose rather than the total quantity given over a period of time.

8. Evidence is presented in support of the view that the use of a small "maintenance dose" of quinidine to maintain the normal rhythm established with larger doses, exerts no appreciable influence on the persistence of the normal rhythm in the ambulatory patient, and that in general more intense quinidine effects are necessary to overcome the influences that precipitate an attack of flutter or fibrillation in the ambulatory patient than to abolish an attack while the patient is at rest.

REFERENCES

1. Lewis, T., Drury, A. N., Ilescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine Upon the Dog's Heart; With Special Reference to Its Action on Clinical Fibrillation of the Auricles, *Heart* 9: 55, 1921.
2. Gold, H., and Modell, W.: The Action of Quinidine on the Heart in the Normal Unanesthetized Dog, *J. Pharm. & Exper. Therap.* 46: 357, 1932.
3. Maynard, E. P.: Five Years' Experience in the Treatment of Chronic Auricular Fibrillation With Quinidine Sulphate, *Am. J. M. Sc.* 175: 55, 1928.
4. Viko, L. E., Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidin Sulphate, *Arch. Int. Med.* 31: 345, 1923.
5. Wilson, F. N., and Wishardt, S. W.: The Effects Produced by the Intravenous Injection of Quinidine and Other Drugs Upon the Mechanism of the Heart Beat, *Tr. Assn. Am. Phys.* 41: 55, 1926.
6. Robinson, G. C., and Draper, G.: II. The Effects of Vagus Stimulation on the Hearts of Children With Chronic Valvular Disease, *J. Exper. Med.* 15: 14, 1912.
7. Gilbert, N. C.: The Increase in Certain Vagal Effects With Increased Age, *Arch. Int. Med.* 31: 422, 1923.
8. Nathanson, M. H.: Site of Hypersensitiveness of the Exaggerated Sinus Caroticus Reflex, *Proc. Soc. Exper. Biol. & Med.* 29: 1037, 1932.
9. Cushny, A. R.: Stimulation of the Isolated Ventricle, With Special Reference to the Development of Spontaneous Rhythm, *Heart* 3: 257, 1912.
10. Gold, H., Modell, W., and Price, L.: An Experimental Study of the Combined Actions of Quinidine and Digitalis on the Heart, *Arch. Int. Med.* 50: 766, 1932.
11. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate on Ventricular Tachycardia, *J. A. M. A.* 92: 1162, 1929.
12. Weiss, S., and Hatcher, R. A.: Studies on Quinidine, *J. Pharmacol. & Exper. Therap.* 30: 335, 1927.
13. Gordon, B., Matton, M., and Levine, S. A.: The Mechanism of Death From Quinidine and a Method of Resuscitation; an Experimental Study, *J. Clin. Invest.* 1: 497, 1925.
14. Lewis, T.: The Value of Quinidine in Cases of Auricular Fibrillation and Methods of Studying the Clinical Reaction, *Am. J. M. Sc.* 163: 781, 1922.

THE IDENTIFICATION OF THE SEPARATE COMPONENTS OF THE QRS COMPLEX

WITH SPECIAL REFERENCE TO THE SO-CALLED PROMINENT Q-WAVE IN
LEAD III

LEWIS M. HURXTHAL, M.D.*
BOSTON, MASS.

THE separate components of the QRS complex in the electrocardiogram are not commonly identified in routine clinical practice. Since the appearance of the "prominent Q_s" as a new sign on the diagnostic

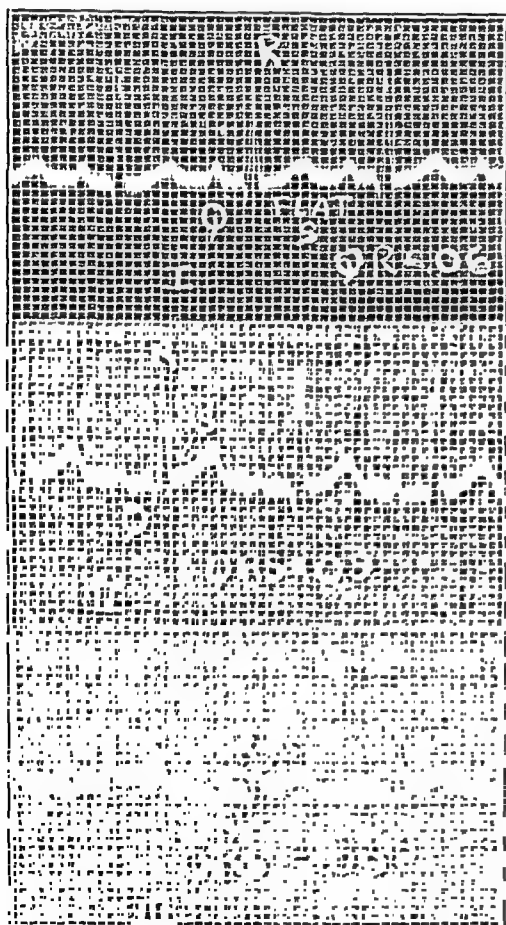


Fig. 1.

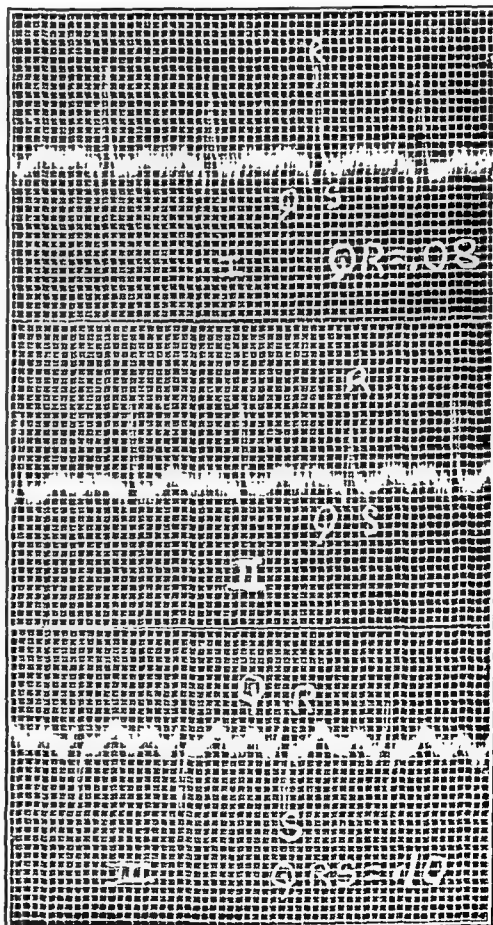


Fig. 2.

Fig. 1.—Illustrating inversion of the Q-wave in Lead I, Lead II, and Lead III. The R-wave here is considered diphasic and the S upright in Lead III.

Fig. 2.—Illustrating inverted Q-wave in Lead I, a high upward S-wave in Lead I, a slightly downward Q in Lead II, and an upright Q and R in Lead III. The S-wave in Lead III is downward. Note depth of downward S₃, which approximates upward slurring of S₁.

*From the Medical Department, Lahey Clinic, Boston, Mass.

horizon, there now appears to be sufficient reason for attempting this differentiation. The purpose of this paper is not to evaluate the significance of a so-called prominent Q-wave in Lead III but to point out that such in reality, rarely occurs. While the initial deflection in Lead III may fill all the requirements set down for its identification,¹ and while this electrocardiographic pattern may have some clinical significance, many of the published records^{1, 2, 3, 4, 5, 6} with the so-called

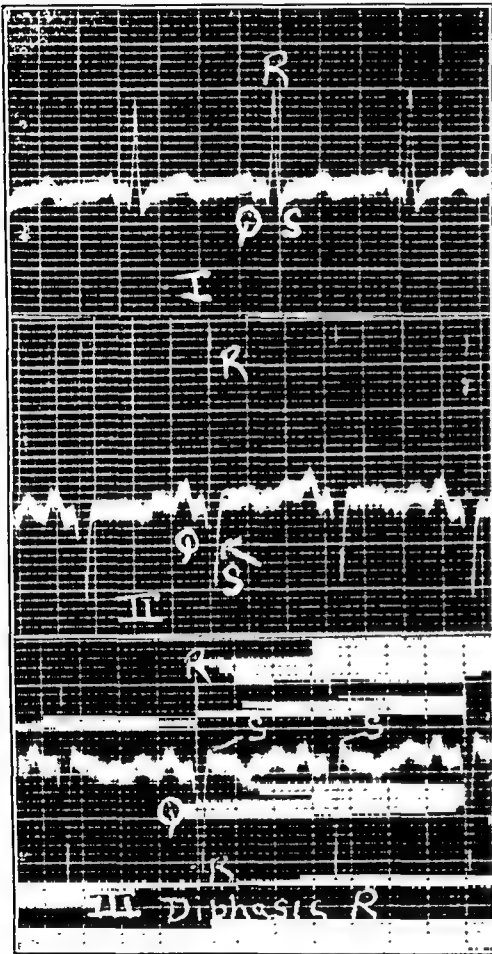


Fig. 3.

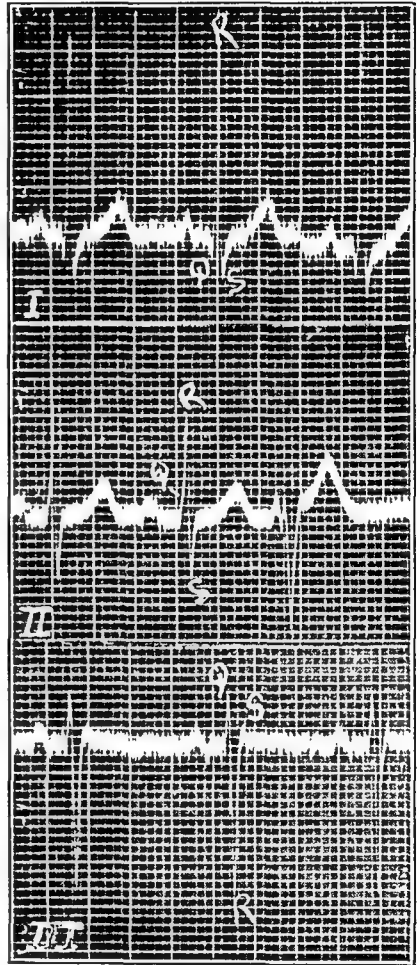


Fig. 4.

Fig. 3.—Showing down Q and S in Lead I and upright R. Further showing down Q in Lead II and diphasic R with slurred down S_2 . In Lead III there is also a down Q-wave and diphasic R-wave. The S-wave is up in Lead III. This is from a case of mitral stenosis. It is unusual that all the Q-waves are downward.

Fig. 4.—Showing a downward Q in Lead I, an upward Q in Lead II slurred with the R_2 , and the upward Q in Lead III with a down R_3 and an up S_3 .

prominent Q_3 will be found to be either (a) a combination of an inverted Q_3 made unduly prominent by a fusion with an inverted R_2 , (b) an inverted R_3 alone with an iso-electric Q_3 or (c) what I believe may be regarded as a diphasic R_3 .

It appears to be the custom to call all initial upward deflections in Lead III R-waves and all secondary down deflections S-waves. Wiggers⁷

adopted Einthoven's designation of inverted initial deflections in Lead III as R-waves, although Lewis named them S-waves. In examining many published records there seems to be no uniformity in naming the various deflections, particularly of Lead III. In order that confusion may be eliminated, particularly with reference to the "prominent Q_3 ," some plan for this purpose should be adopted.

In records where all three waves can easily be identified, it will be found that the duration of each wave is practically constant in each

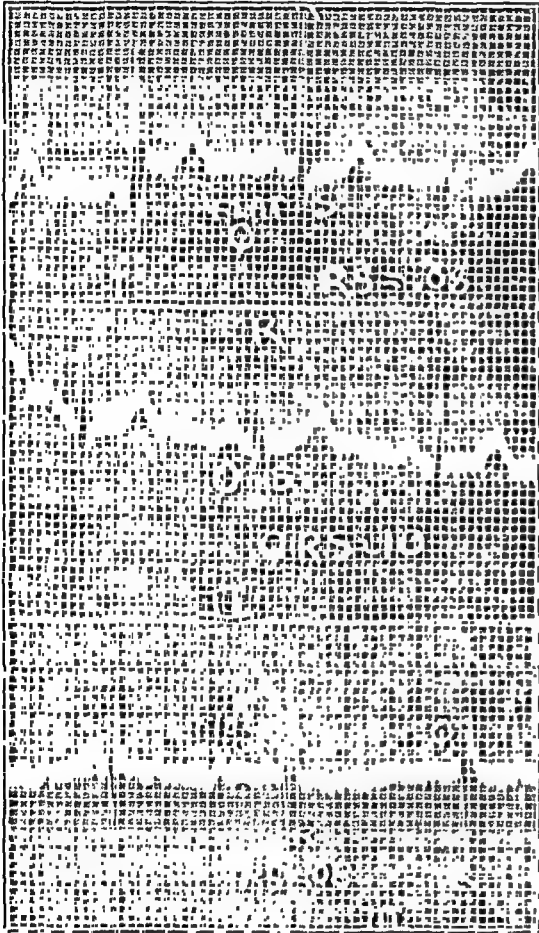


Fig. 5.

Fig. 5.—Showing no evident Q-wave in Lead I (iso-electric Q phase), a definite Q-wave in Lead II, pointing downward, and what appears to be a prominent Q_3 which is in reality a diphasic R-wave with an initial down deflection and a short up S-wave.

Fig. 6.—Illustrating an up Q-wave in Lead I, an upward Q-wave in Lead II, and apparently an upward Q-wave of Lead III. This is unusual.

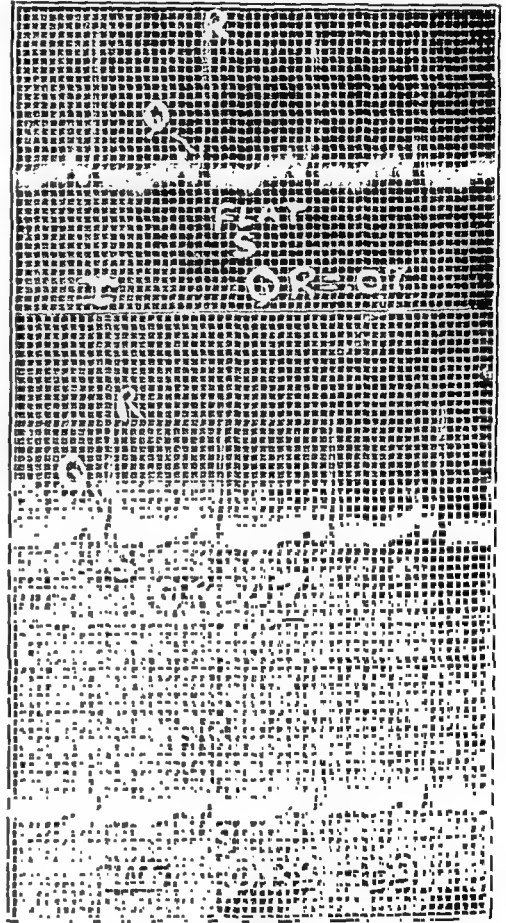


Fig. 6.

lead and thus the duration of QRS is constant. The Q-wave in Lead I is apparently identified only when it points downward: the same usually holds true for the Q-wave in Leads II and III, although upward Q-waves in Lead III are occasionally designated.

In left axis deviation the Q-wave in Lead I is almost always well marked and points down. In these cases, a distinct upright initial de-

flection will be found in most instances in Lead III. In contrast to this up Q_3 in left axis deviation the Q-wave in Lead III of right axis deviation will be downward. If Lead I is examined in right axis deviation, a distinct initial upward deflection may be found in case the R-wave is inverted. If the R-wave in Lead I is slightly upright in right axis deviation, a slurring at the origin of R will be found. It is reasonable to assume this to be the fusion of an upright Q and R.

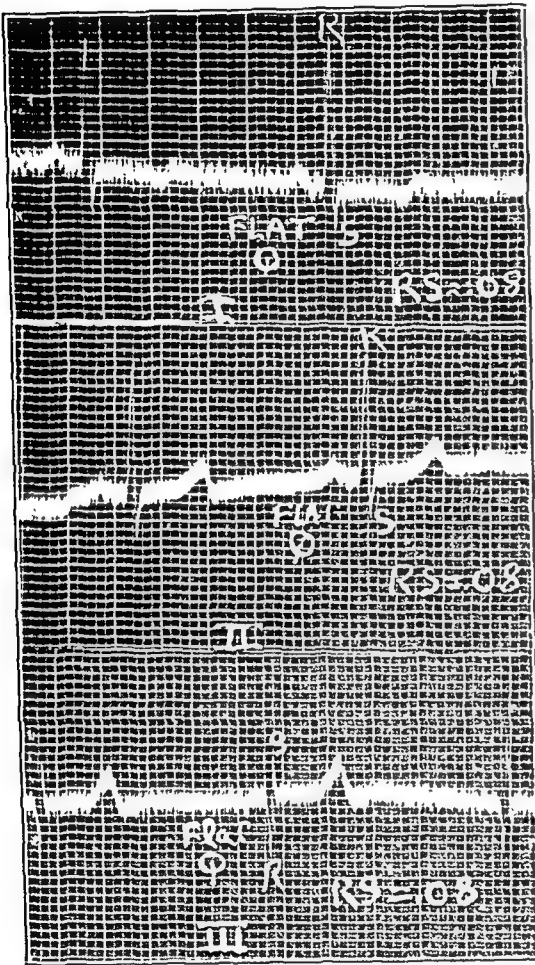


Fig. 7.

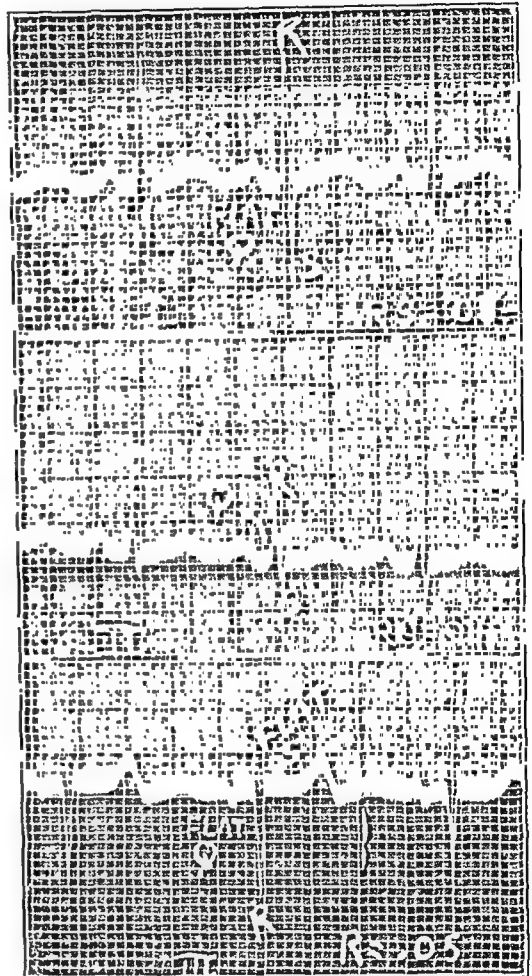


Fig. 8.

Fig. 7.—Illustrating a flat Q-wave in Leads I, II, and III (iso-electric Q phrase). The apparent Q-wave in Lead III is an inverted R-wave. The S_2 wave here is upright.

Fig. 8.—This shows a flat Q-wave in Lead I, a slightly up or flat Q-wave in Lead II and a flat Q-wave in Lead III. The apparent initial downward deflection simulating an inverted prominent Q-wave is an R-wave and the S_2 wave is flat. The R phrase of Lead I is diphasic. The down deflection marked "S" in Lead I is too deep for an S and if it were an S, there should be an up S phase in Lead III. Compare this record with Fig. 7, from the same patient at a later date (coronary thrombosis) in which a down S_1 and an up S_2 are easily recognizable.

If the QRS group is divided into time sections rather than deflections, and the first phase of the QRS span be considered due to Q whether it be up, iso-electric, or down, and if the R and S sections are regarded in the same manner, there should be no difficulty in many

and in fact, in most instances of being able to recognize clearly the separate components of the QRS complex.

If the so-called prominent Q-waves of Lead III are subjected to analysis in this way, it will be found that all such "Q" waves have a greater duration than is usual for a normal Q-wave, and that the actual time is often one-half or more of the total QRS duration.

Einthoven's law, $\text{Lead I} + \text{Lead III} = \text{Lead II}$, is applicable to the individual components of the QRS group, and it would appear that such

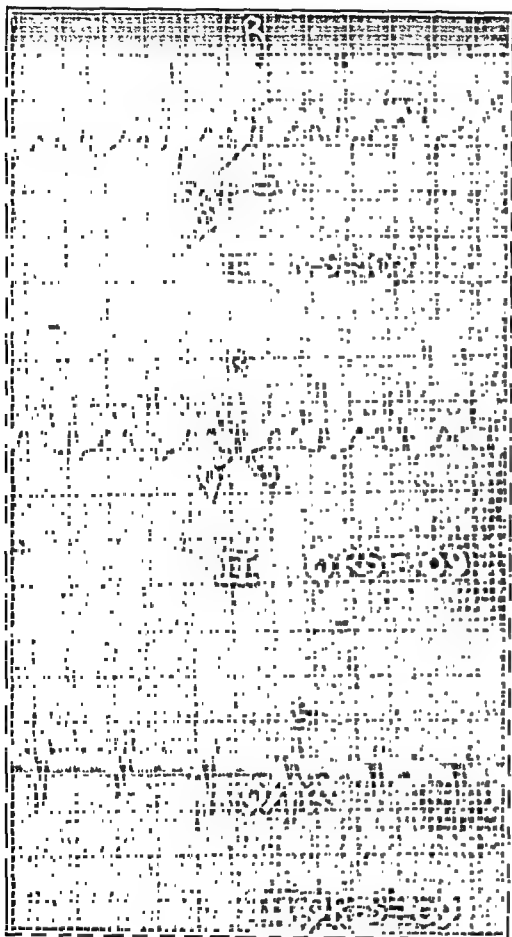


Fig. 9.

Fig. 9.—Showing a flat Q-wave in Lead I, a definitely down Q in Lead II, and a Q-wave in Lead III. The R-wave is diphasic and the initial down deflection of the R-wave is fused with the down Q-wave.

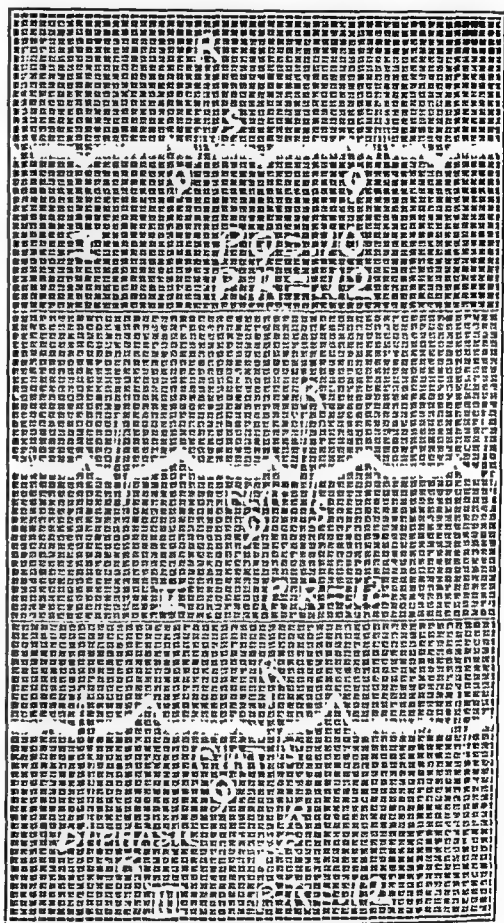


Fig. 10.

Fig. 10.—Showing a down Q in Lead I and an up S in Lead I fused with R-wave of Lead I. The R-wave in Lead III is diphasic, the S-wave in Lead III, inverted. The Q is upward in Lead III and fused with the R-wave.

application is often helpful for the correct identification of the Q-waves. In routine clinical electrocardiographic records, this law can be applied to the separate phases of the QRS group. The inability to determine this is usually due to the effect of somatic tremor or other irregularities or abnormalities which make it difficult to separate the various components.

The duration of the Q-phase can be considered usually as about one-half the duration of either R or S, so that in the total QRS phase of 0.10, the Q phase may be estimated as 0.02 seconds. By finding the greatest QRS duration of the leads and measuring backward or forward from the beginning of the Q or the end of the S in other leads,

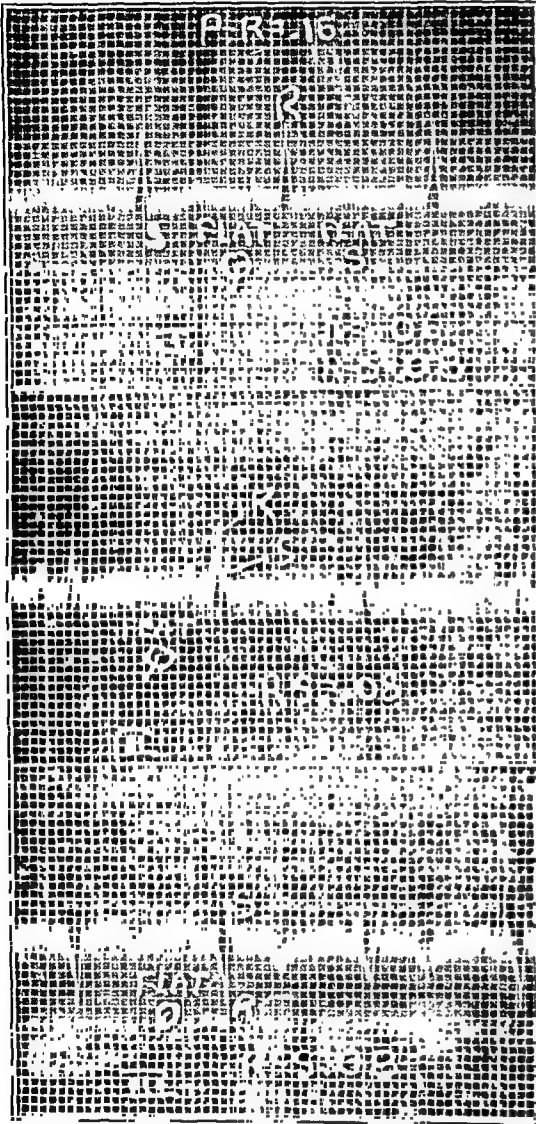


Fig. 11.

Fig. 11.—Showing again absent Q-waves in all leads and an upright R-wave in Lead I, with a flat or slightly down S-wave in Lead I. Two upright waves in Lead II, which measure to be the R- and S-waves, and then the inverted R of Lead III with the upright S in Lead III.

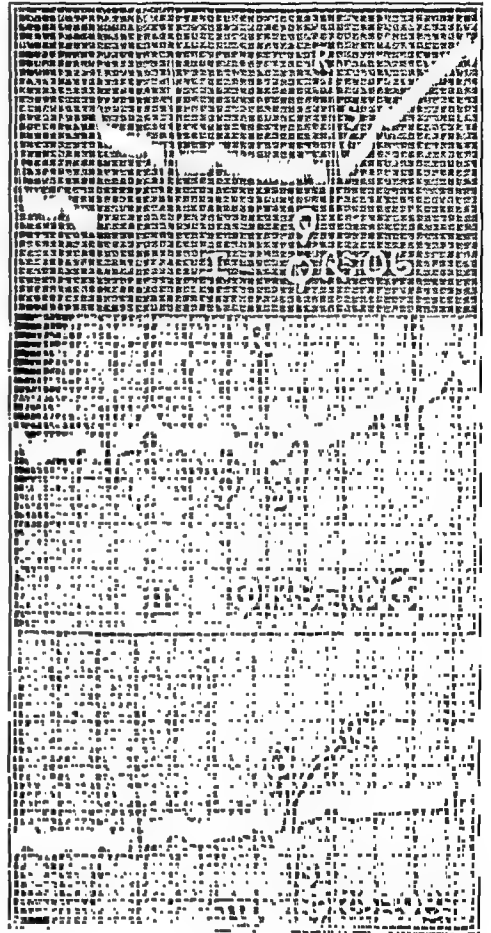


Fig. 12.

Fig. 12.—Illustrating inverted Q-wave pointing downward in Lead I and upright Q in Lead III. Note also the slurring of the upright S in Lead I with the R-wave, the height of which approximates the depth of the down S₃-wave.

the true QRS section can be laid off, and the direction of the deflection, if any, for each section can be determined.

Measurements of value may be made at times from the peak of the P-wave, if the heart rate is the same in all leads. Of course, simul-

taneous records of Leads I and III would be the best way to identify the initial waves, although it is not often necessary. For example, if a well-marked downward Q is found in Lead I, there is little likelihood of the Q pointing downward in Lead III. In such an instance, the first downward deflection in Lead III may be considered an inverted wave of the R phase, and the Q section would then be iso-electric.

In the majority of instances, the Q, R, or S phase will be either positive, negative, or iso-electric. There are times when the R-wave will

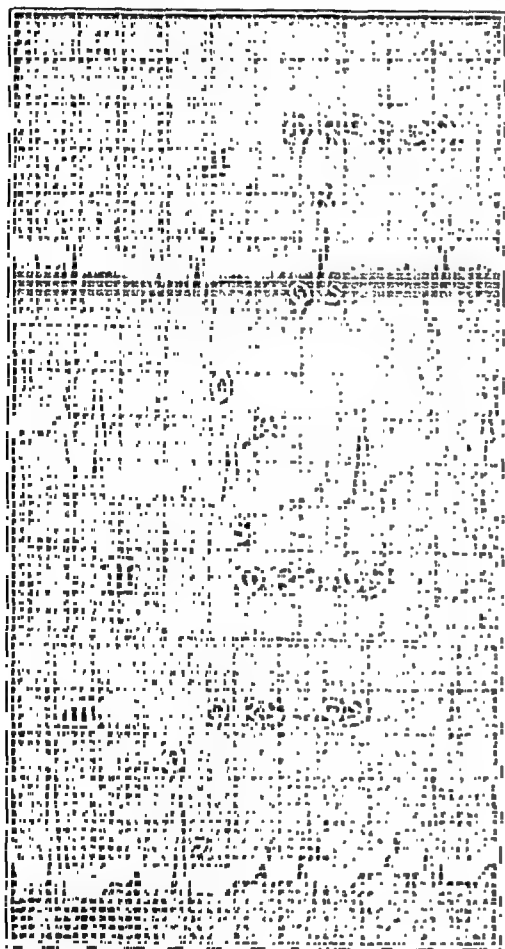


Fig. 13.

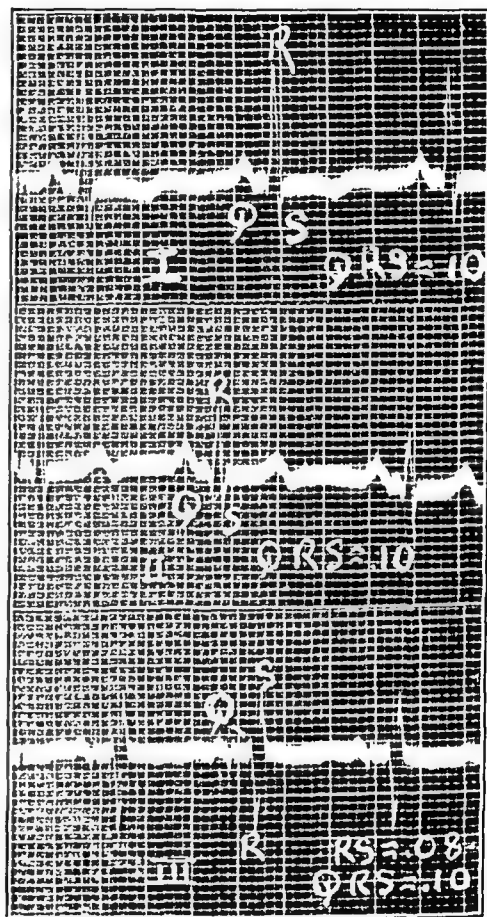


Fig. 14.

Fig. 13.—Showing a down Q_i and up R_i, and a down S_i. In Lead II the Q-wave is up and fused with the R-wave. In Lead III the Q is also fused with the R, and the R is partially diphasic, and the S-wave in Lead III is upright.

Fig. 14.—Showing what might be interpreted as a prominent Q₂. The slightly up initial deflection in Lead III is the Q phase, and approximates the down Q excursion in Lead I. The R-wave in Lead III is diphasic and accounts for the apparently large up S phase, ordinarily called an R₂-wave.

have to be considered diphasic, yet there is no reason why this should not occur. Rarely do the Q and S phases have prominent deflections, if considered from this point of view. The R phase will be found to account for most of the great excursions of the QRS complex. Thus, if there appears to be both a positive and a negative deflection in the usual

time period of the R phase, the R-wave can thus be considered diphasic. Many instances of so-called splintered QRS complexes can be analyzed in this light.

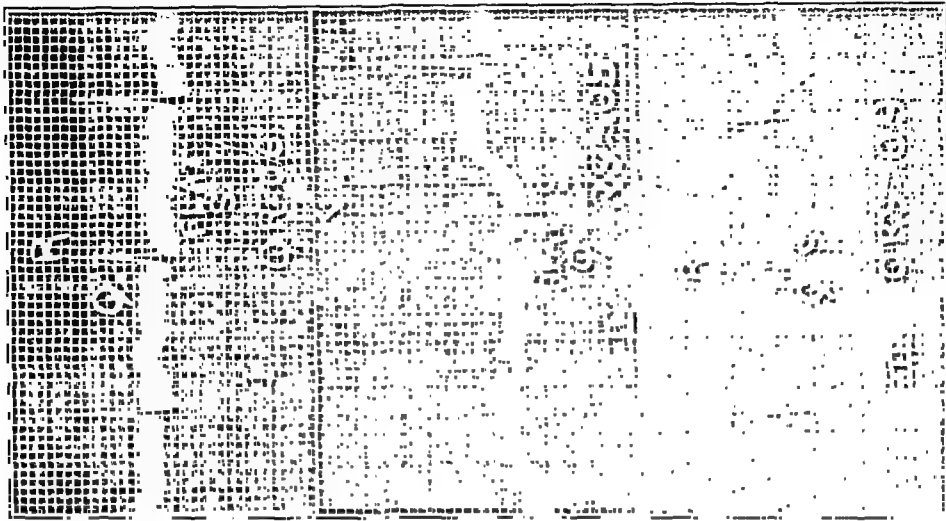


Fig. 17.

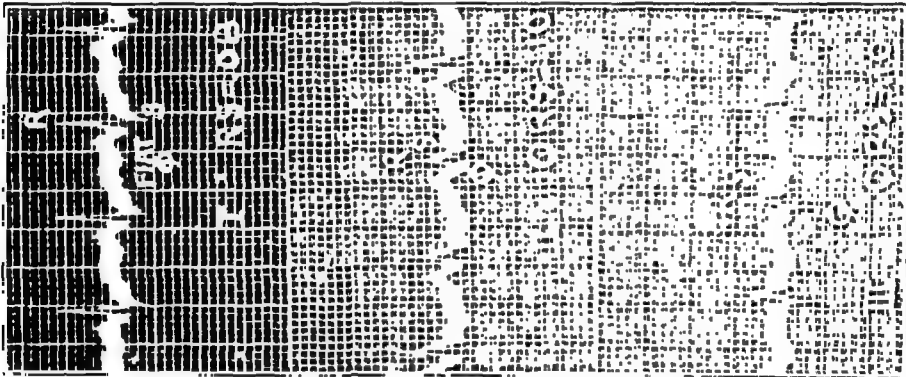


Fig. 16.

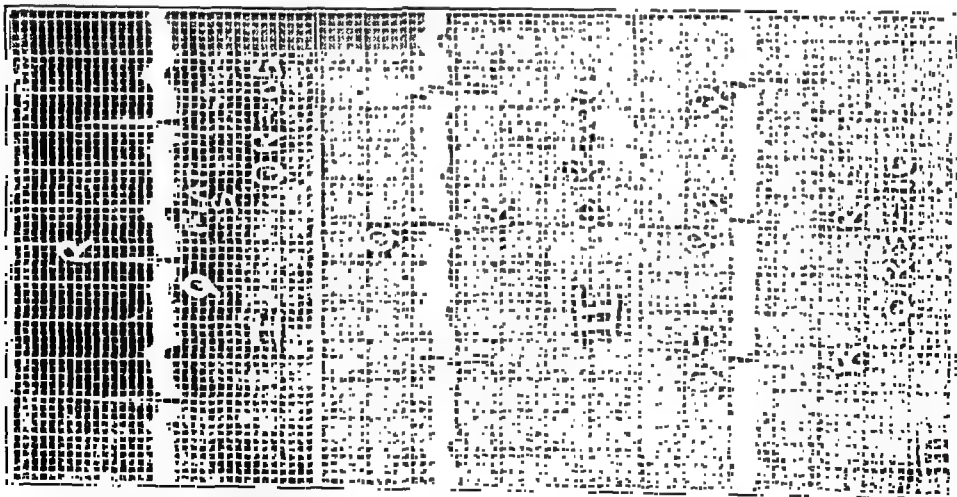


Fig. 15.

Fig. 15.—Showing opposite directions of the Q_1 and Q_3 . The R-wave of Lead II is diphasic.

Fig. 16.—Showing splintered QRS of Leads II and III, also probably a true prominent Q_3 -wave.

Fig. 17.—Showing an up Q phase in Lead I, causing slurring. Note absence of slurring in Lead III where the Q is opposite in direction to the R.

It seems possible that more information might be obtained in studying electrocardiograms from this viewpoint. It raises several interesting questions; for example, if the Q-wave is normally downward in

Lead I, what causes it to point upward in Lead I when right axis deviation is not present? Does the reversal of the Q direction without change

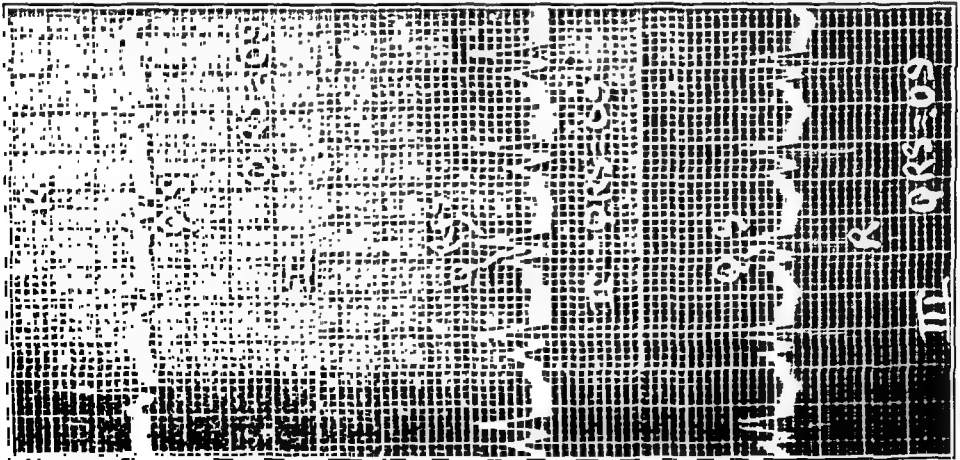


Fig. 18.

Fig. 18.—Prominent up Q₁, diphasic R₂ rendering the S₃-wave unduly prominent.

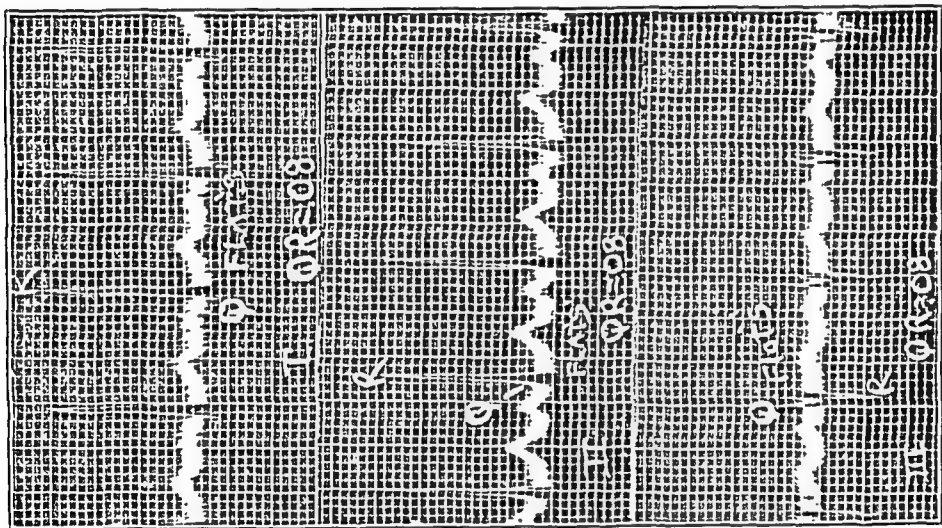


Fig. 19.

Fig. 19.—Illustrating an up Q₁-wave, a diphasic R₂-wave, and flat S phase in all leads.

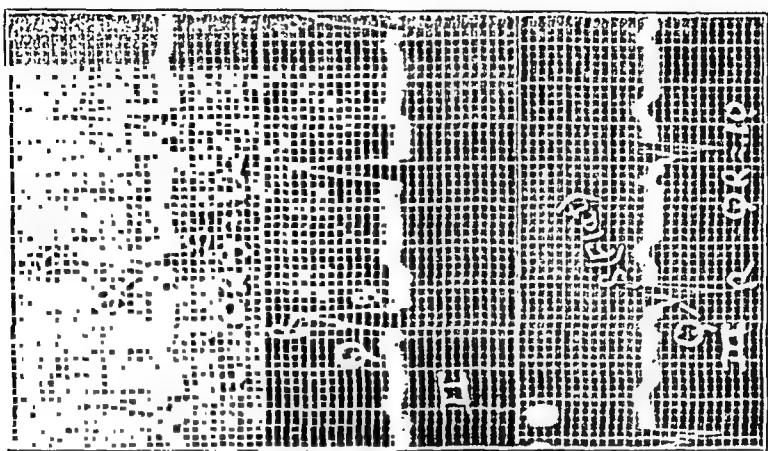


Fig. 20.

Fig. 20.—Showing slurring QRS in Leads I and II, caused by wide Q section. Note the wide downward Q-wave of Lead III.

in axis deviation indicate disease in the septum? These and many other questions have come to mind in going over many tracings. Such an analysis is being undertaken. Illustrative records are appended.

CONCLUSIONS

1. The various components of the QRS are not difficult to identify in the majority of electrocardiograms.
2. It is suggested that the QRS interval be divided into three sections, and each section described as iso-electric, positive, negative, or diphasic.
3. Prominent Q_3 -waves are rare. They are confused with inverted waves of the R phase of the QRS complex.

REFERENCES

1. Pardee, H. E. B.: The Significance of the Electrocardiogram, With Large Q_3 , Arch. Int. Med. 46: 470, 1930.
2. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction, Heart 14: 195, 1928.
3. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Medicine 8: 245, 1930.
4. Willius, F. A.: Occurrence and Significance of Electrocardiograms Displaying Large Q-Wave in Lead III, AM. HEART J. 6: 723, 1931.
5. Fenichel, N. M., and Kugell, V. H.: The Large Q-Wave of the Electrocardiogram: A Correlation With Pathological Observation, AM. HEART J. 7: 235, 1931.
6. Strauss, S., and Feldman, L.: The Significance of the Large Q-Wave in Lead III, Am. J. M. Sc. 185: 87, 1933.
7. Wiggers, C. J.: Principles and Practice of Electrocardiography, St. Louis, 1929, The C. V. Mosby Co.

CLINICAL DOSE AND EFFECTS OF DIGITALIS ASSAYED BY THE PIGEON METHOD*†

A. B. STOCKTON, M.D.

SAN FRANCISCO, CALIF.

PREDICTION of the clinical dose of digitalis by transfer to man of the "pigeon emetic," or minor toxicity, dose was tested previously on a group of normal subjects.¹ It was found that the intravenous emetic dose of digitalis per kilo of pigeon approximated the total clinically effective oral dose per kilo of man. This work has been continued in order to ascertain if this dosage-agreement held also for patients with cardiac disease. The matter was tested on 67 patients, and 10 normal subjects, with results believed to be worthy of record.

All the patients used had congestive heart failure; 30 of the 67 had decompensation associated with auricular fibrillation. During the investigation the patients were confined at absolute rest to their beds in the hospital. Fluid intake and urine output were measured daily. Accurately weighed quantities of powdered digitalis were administered in capsules. Two leaves of similar potency (Upsher-Smith) were tried.

TABLE I

CLINICAL RESULTS WITH DIGITALIS ASSAYED BY THE PIGEON METHOD

	LEAF I	LEAF II
Pigeon Emetic Dose (predicted total clinical dose) (mg./kg.) - E	14.0	15.0
Clinically Effective Dose, 67 patients (mg./kg.) - C	17.7	16.6
Ratio C/E	1.2	1.1
Slowing of Pulse (beats per minute)	28	24
Diuretic Action (per cent of 27 edematous patients)	77	50
Nausea or Emesis (per cent of 67 patients)	42	18
Symptoms of Digitalis Poisoning (per cent of 67 patients)	14	12
Abnormal Cardiac Rhythm Due to Poisoning (per cent of 67 patients)	8	6

An intensive method of medication was followed throughout as in the previous study; i.e., one-half the estimated total dose was administered at once, one-fourth at the end of four hours, and thereafter one-eighth every three hours until definite signs of digitalis action occurred. Accordingly, errors in clinical dosage plus or minus 12 per cent would be expected, but this was regarded as satisfactory enough under the conditions. The criteria of digitalis action were: slowing of the pulse;

*From the Department of Pharmacology and of Medicine, Stanford University School of Medicine, San Francisco.

Supported, in part, by grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

†Presented before the Society for Experimental Biology and Medicine, Pacific Coast Branch, February 8, 1933.

decrease in venous pressure, as indicated by decreased vein-distention and by venous pressure determinations; relief from dyspnea, general improvement of the patient; increased diuresis in edematous patients; minor toxic actions, such as loss of appetite, nausea, and vomiting; and cardiac arrhythmias. A summary of the essential data and comparisons is presented in Table I; the results in all cases represent averages.

COMPARATIVE DOSES

Leaf I, assayed by the pigeon method, had a M.Em.D. (minimum emetic dose) of 14 mg. per kilo. The average dose required for clinical improvement in 30 patients was 17.7 mg. per kilo, or 26 per cent more than the dose estimated by the pigeon method. The range of clinically effective doses was wide; between 29.6 and 10.2 mg. per kilo, a difference exceeding 190 per cent. Wide variation in clinical dosage of digitalis is a matter of common knowledge, and is due to a number of uncontrollable factors, such as individual susceptibility, irregularities of gastrointestinal absorption, etc.

Leaf II had a M. Em. D. of 15 mg. per kilo. The clinically effective dose, assayed on 27 patients, was 16.6 mg. per kilo, or 11 per cent more than the pigeon emetic dose. The range of clinical doses again proved large; i.e., from 6 to 28.6 mg. per kilo, a difference of over 370 per cent.

In the standardization of digitalis with pigeons it was observed by Hanzlik² that the minimum emetic dose was somewhat higher for males than for females. No such difference in sexes was observed in human subjects, the average dose of digitalis for 35 males being 17.6 mg., and for 32 females 17.9 mg., per kilo.

Ten other subjects with apparently normal cardiovascular systems were given Leaf I. The average dose which caused slowing of the pulse, anorexia, and slight nausea was 24 per cent higher than in patients with congestive heart failure. The normal subjects required 22 mg. per kilo as compared with 17.7 mg. per kilo for those with pathological conditions.

According to these results, the clinical doses of the two samples of digitalis leaves had a fairly constant ratio to the pigeon emetic dose, namely, 1.2 and 1.1; unity would indicate perfect agreement. Accordingly, the pigeon dose gives all that could be expected of a bio-assay method on animals. While any bio-assay method is useful for comparing the potency of one digitalis product with another, the choice would naturally fall on the easiest and most economical method, and such is the pigeon method. Burn³ has shown that the pigeon method is as satisfactory as the cat method for bio-assay purposes. Confirmations of the value of the pigeon method have also been made by Guidi⁴ and by Carratala.⁵ From the clinical data obtained, it is apparent that the pigeon-emetic dose in milligrams per kilo may be transferred directly to

milligrams per kilo body weight of patient, since the pigeon-clinical dose ratio approaches unity. The margin of therapeutic safety would be indicated by the ratio of pigeon-emetic and fatal doses.

Comparisons of the clinically effective doses with cat-fatal doses⁶ have not been made by me, since the assays with cats in this laboratory have been too variable,⁷ and the median doses have exceeded those frequently reported by others.⁸ For instance, the cat-fatal dose of Leaf I was a median of 108 mg. per kilo (range 87 to 190 mg.; 8 cats), while the fatal dose given on the container was 88.5 mg. per kilo. The ratio of the predicted clinical dose from the former cat dose to that found would be 0.55, and from the latter cat dose, 0.67, which is poor as to agreement of values and as to comparability with the pigeon-clinical ratio. Assays on significant numbers of cats, comparable with the dozens of pigeons used in our assays, are not practically feasible, and therefore, the pigeon doses are more accurate. The practice of selecting doses is scientifically unjustifiable with any bio-assay method.

CLINICAL EFFECTS

The great range of effective dosage in man has been observed before. Obviously, there is no method of bio-assay which can determine the dose for the individual patient when variations of nearly 200 to over 300 per cent occur with the same leaf in different human subjects. In spite of the most accurate assay, each patient must be observed closely for signs of digitalis action. The dose must be determined solely by the clinical response of the individual patient, regardless of the potency of the digitalis. The value of bio-assay lies in the reduction of error in dosage from several thousand per cent (between various digitalis preparations) to two or three hundred per cent (due to variations in individual susceptibility). The pigeon-emetic dose, which is a minor toxicity dose, should come close to indicating the probable limit of the total clinical therapeutic dose, as indeed it appears to do, according to the typical signs and symptoms of digitalis action observed in this study. Known conditions, such as altitude, which increases the emetic and toxic actions of digitalis, should be taken into account when estimating the clinical dose.⁷

Slowing of the pulse is one of the most valuable practical signs of digitalis action. This slowing occurs also in normal persons, although the dosage required to produce the change is somewhat higher than in those with a pathological condition.^{1, 10}

Nausea, and especially vomiting, are to be avoided if possible. Sixty per cent of all my patients (Leaf I, 48 per cent and Leaf II, 12 per cent) experienced loss of appetite or nausea, while 28 per cent vomited one or more times. Starnotti,⁹ who tried pigeon-emetic doses of a number of digitalis specialties in 15 patients, observed similar symptoms in

40 per cent of his patients. He stated that his clinical experiments demonstrated the reliability of the pigeon method of digitalis assay, but he doubted the advisability of the intensive administration as a standard system of dosage.

Of the 67 patients, only 8 experienced more or less intense digitalis poisoning; 4 of these showed cardiac irregularities, consisting of extra-systoles, heart-block, and 1 showed bigeminal rhythm. Three of these patients were later found to have had digitalis before entering the hospital, but poisoning in the other 5 patients was due to failure to adhere to the proper technic of medication, and could have been avoided.

Diuretic action occurred in 64 per cent (average of 77 and 50 per cent) of all patients having congestive heart failure and edema. No increase in urine output occurred in normal subjects receiving digitalis. Digitalis-diuresis has been discussed in a previous paper.¹⁰

CONCLUSIONS

1. The ratios of clinically effective doses of 2 digitalis leaves, in 67 patients, to the pigeon-emetic doses were found to be 1.2 and 1.1. The actual clinically effective doses were 17.7 and 16.6 mg. digitalis per kilo body weight, a remarkably good agreement with the pigeon doses.

2. About 60 per cent of all the patients showed minor symptoms of toxicity, such as nausea, and 28 per cent vomited, after oral doses of digitalis equal to the intravenous pigeon-emetic dose per kilo body weight. Only 8 of the 67 patients showed evidences of digitalis poisoning with this dosage. These side-actions testify that the pigeon-emetic dose results in definite systemic absorption and action of digitalis.

3. The pigeon method fulfills all that can be reasonably expected of a bio-assay method on animals, which would predict the probable full therapeutic dose, and it is the easiest and most economical of all bio-assay methods.

4. The wide range of dosage required to secure full therapeutic effects of digitalis in man emphasizes the importance of close clinical observation during medication, even though a standardized preparation is used.

REFERENCES

1. Stockton, A. B., and Hanzlik, P. J.: *J. Pharmacol. & Exper. Therap.* 35: 393, 1929.
2. Hanzlik, P. J.: *J. Pharmacol. & Exper. Therap.* 35: 363, 1929.
3. Burn, J. H.: *J. Pharmacol. & Exper. Therap.* 39: 221, 1930.
4. Guidi, G.: *Rassegna di terap. e pat. clin.* 2: 129, 1930.
5. Carratala, R. E.: *Semana méd.* 2: 1606, 1931.
6. Hatcher and Brody: *Am. J. Pharmacol.* 82: 360, 1910.
7. Lehman, A. J., and Hanzlik, P. J.: *Proc. Soc. Exper. Biol. & Med.* 30: 140, 1932.
8. Eggleston, C.: *Arch. Int. Med.* 16: 1, 1915.
9. Starnotti, C.: *Rassegna di terap. e pat. clin.* 2: 385, 1930.
Rev. sud-am. de endocrinol. 14: 349, 1931.
10. Stockton: *Arch. Int. Med.* 50: 480, 1932.

THE EFFECT OF ADENOSINE ON CARDIAC IRREGULARITIES IN MAN*

A. JEZER,† M.D., B.S. OPPENHEIMER, M.D., AND S. P. SCHWARTZ, M.D.
NEW YORK, N. Y.

IT HAS been recently observed by Drury and Szent-Gyorgyi that adenosine may restore sinus rhythm in the heart of animals in which auricular fibrillation has been produced experimentally. As the use of such a drug which could restore the normal mechanism of the heart in man would be of great value, we undertook the investigation of the action of the drug in several patients with abnormal rhythms of the heart.

Adenosine is a yeast nucleic acid derivative, and its chemical and its biological properties have already been described by Drury and Szent-Gyorgyi.¹ The effect of adenosine and its related compounds may be summarized as follows.

These drugs slow the rate of beating in normal sinus rhythm. They impair conduction from auricle to ventricle, arrest experimentally induced auricular fibrillation, shorten the refractory period in high rates of beating, and improve slowed rates of intra-auricular conduction. They also dilate the coronary, renal and splanchnic arteries and cause a drop in arterial blood pressure. The effect is transient and is completely over in from forty to sixty seconds. In the guinea pig this group of drugs produces a partial heart-block. Atropine does not abolish the disturbances in heart rhythm induced by these drugs. Barium salts do, however, inhibit the action of these related drugs in the animal.

Honey and his coworkers² were not successful in arresting auricular fibrillation in man after the administration of 50 mg. of adenosine. They do not report, however, whether the auricular fibrillation in their cases was paroxysmal or permanent. It is important to appreciate this, since only the transient type of auricular fibrillation responds to adenosine, as shown by the experimental work of Drury and Szent-Gyorgyi.

METHOD OF STUDY

Adenosine was administered to seven patients with heart disease and to one patient with pulmonary tuberculosis, all of whom developed ectopic rhythms while under observation at the Montefiore Hos-

*From the Medical Division of the Montefiore Hospital, Service of Dr. B. S. Oppenheimer.

†Benjamin Rosenthal Fellow.

pital. In none of the cases were the ectopic rhythms the result of drug therapy. Four of the patients, one with auricular fibrillation, two with auricular tachycardia, and one with a supraventricular type of tachycardia, had been observed during previous paroxysmal seizures of these arrhythmias. Pressure over the carotid artery restored normal sinus rhythm in only one of the eight cases with arrhythmias.

The doses of adenosine varied from 5 to 50 mg. Doses of less than 15 mg. were not effective even when given intravenously. The subcutaneous and intramuscular administration of the drug up to 50 mg. was also ineffective. All of the observations which are being reported followed the intravenous administration of the drug.

Control electrocardiograms were obtained before, during, and after the administration of the drug for periods varying from one to three hours.

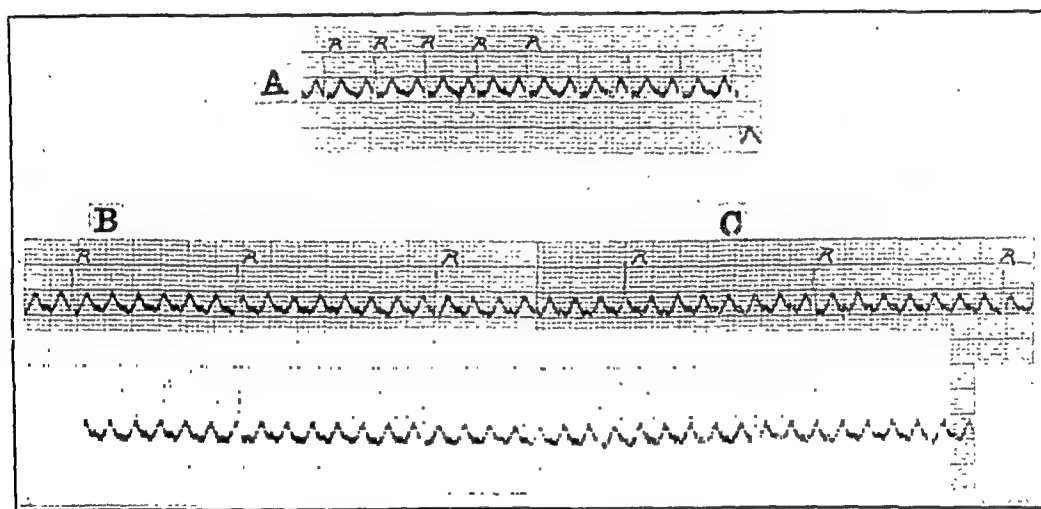


Fig. 1.—The effect of adenosine on flutter of the auricles. A, Control before adenosine; B and C, after adenosine.

The following is a report of some of the correlated observations we made during this investigation.

OBSERVATIONS

I. *The Effect of Adenosine on Auricular Flutter.*—A female, twenty-five years of age, with chronic rheumatic heart disease and mild congestive heart failure, developed a paroxysm of flutter of the auricles with the ventricles beating at the rate of 210-230 per minute and the auricles beating at the rate of 420 per minute.

Shortly after the onset of the paroxysm 35 mg. of adenosine were given to her into the antecubital vein. Ten seconds after the injection the ventricular rate suddenly dropped from 210 (Fig. 1 A) to 80 beats per minute and continued to beat between 80 and 100 beats per minute for the next forty seconds (Fig. 1 B, C). Then the ventricular rate gradually increased until it reached its pre-injection level of 210 beats per minute, twenty seconds later.

The electrocardiogram shows a marked increase in block, appearing ten seconds after the injection (Fig. 1 B) and lasting sixty seconds. The rate of the flutter

of the auricles is not altered (Fig. 1 *B, C*). The greatest increase in block occurs fifteen to thirty-five seconds after the injection, when the ventricles responded to every seventh or eighth impulse which arises in the auricles (Fig. 1 *C*). The block then diminishes until the 2:1 block is re-established at the end of sixty seconds. The ventricular complexes are not altered in shape, size, or form.

Comment.—The effect of adenosine in auricular flutter is predominantly on the junctional tissue, as is shown in the accompanying electrocardiograms. There is no effect on the rhythm of the auricles in this case. This is in agreement with the conclusions drawn from the experimental work in animals where the influence of adenosine is principally on the sino-auricular and auriculoventricular nodes.

II. *The Effect of Adenosine on Paroxysmal Auricular Fibrillation.*—A male, aged fifty years, with chronic coronary vessel closure developed frequent seizures of paroxysmal auricular fibrillation. Large doses of digitalis did not diminish the frequency or the duration of the attacks. Pressure over the carotid arteries had no effect on the rhythm.

Soon after the onset of one of the paroxysms of irregular rhythm we administered intravenously 20 mg. and 30 mg. respectively of adenosine. The 30 mg. dose was given one-half hour after the administration of the smaller dose which did not produce any clinical or electrocardiographic changes. The administration of larger dose of the drug was followed by a short period of bradycardia, but the rhythm of the auricles was not altered.

Soon after the onset of another of the paroxysms of the irregular rhythms, we administered intravenously 45 mg. of this drug. Ten seconds after the administration of this dose the patient complained of precordial pain, giddiness, and faintness. The heart rate suddenly dropped from 100 beats per minute to 40 beats per minute, and at fifteen seconds after the injection the heart sounds became inaudible and the pulse imperceptible for a period of four seconds. Then the heart sounds were again heard beating at a slow rate and gradually increasing in speed until at the end of forty-five seconds the heart rate was again at its pre-injection level. The precordial pain, giddiness, and faintness disappeared when the heart rate had increased to 60 beats per minute. The rhythm remained irregular.

The electrocardiograms show a lengthening of the R-R period from 0.5-0.7 seconds to 0.7, 0.9 and 1.6 seconds in successive beats followed by a period of asystole of the ventricles of 4.6 seconds' duration. A normal supraventricular complex ends the asystolic period and is followed by an ectopic beat, arising in the ventricles. The ventricular beats now appear more regularly at intervals of from 1.4 to 1.9 seconds until 52 seconds after the injection when the R-R intervals gradually decrease to the pre-injection ventricular rate. The fibrillation of the auricles is not affected.

Comment.—In a patient suffering from paroxysmal auricular fibrillation the auriculoventricular block was markedly increased for a period of 60 seconds after the administration of the drug. At 20 seconds the ventricles did not respond for a period of 4.6 seconds, and then the ventricles beat at the rate of only 30 to 40 per minute. The auricles continued to fibrillate.

III. *The Effect of Adenosine on Sinus Rhythm.*—In the same patient, thirty-five mg. of adenosine were given during the phase of normal sinus rhythm. The patient complained of marked giddiness, precordial pain, and faintness beginning about ten seconds after the injection. This lasted for 20 seconds. During this period the pulse was imperceptible (Fig. 2 *B*) and the heart sounds were not heard. The first ventricular contraction after the pause was followed quickly by a second pause.

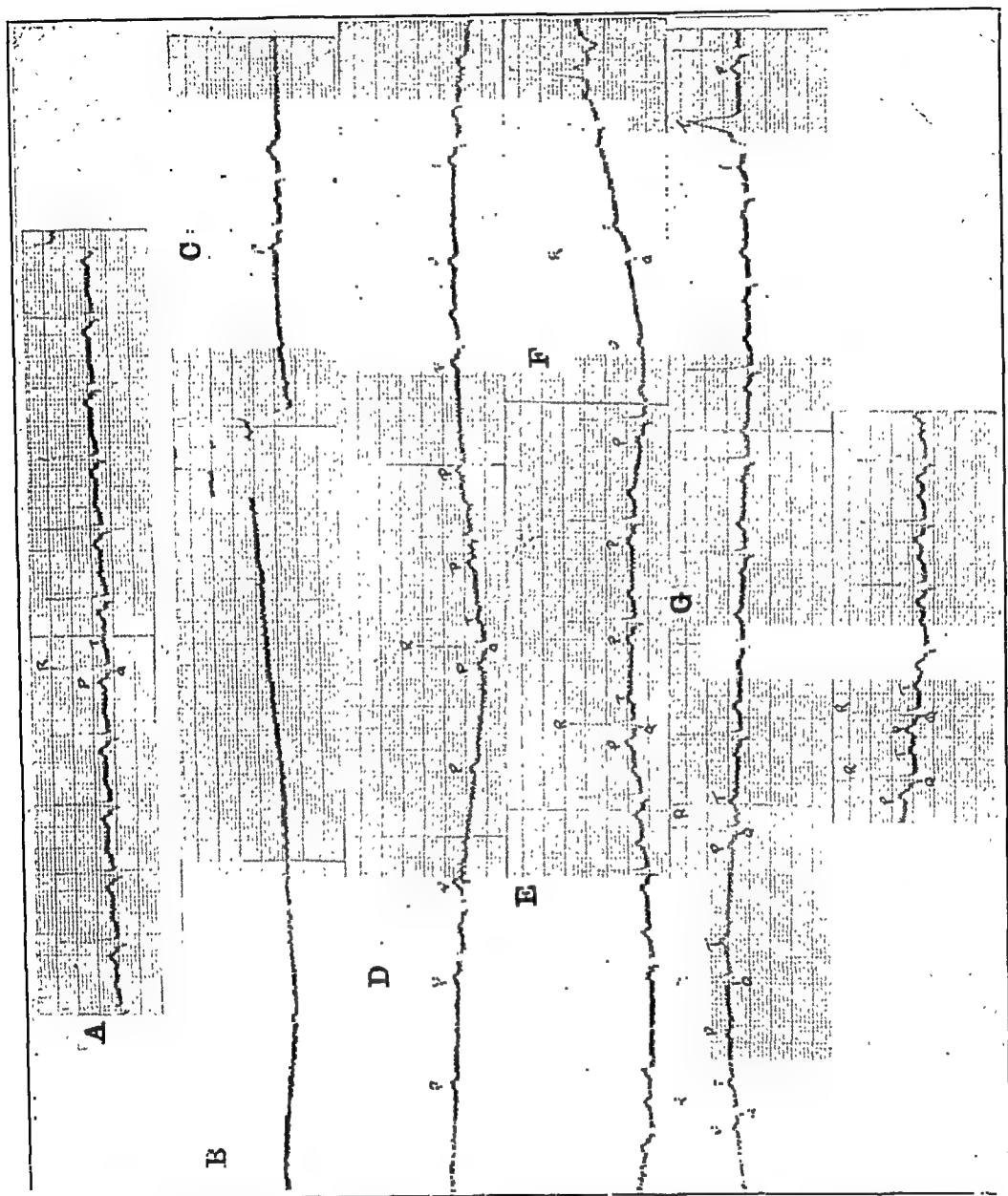


Fig. 2.

Fig. 2.—The effect of adenosine on paroxysmal sinus rhythm. *A*, Before adenosine; *B*, ten seconds after 35 mg. of adenosine; *C*, fifteen seconds after adenosine; *D*, twenty-three seconds after adenosine; *E*, forty seconds after adenosine; *F*, forty-five seconds after adenosine; *G*, fifty-five seconds after adenosine.

Then there was another pause for 3 seconds. During this period the patient complained of the same symptoms as described above (Fig. 2 *C*). The pulse continued beating at the rate of 25-50 beats per minute for 25 seconds; then it increased in rate to the pre-injection level (Fig. 2 *C, D, E*).

The electrocardiograms show a period of ventricular asystole of 0.2 seconds (Fig. 2 *B*) followed by periods of 2-3 seconds of ventricular asystole (Fig. 2 *C*). The auricles continued beating at the rate of 90 per minute and each second to third beat was followed by a ventricular complex (Fig. 2 *D*). The P-R interval remained constant at 0.17-0.2 seconds. The normal auriculoventricular conduction was restored for a short period (Fig. 2 *E*), following which the auricular rate was slowed from 90 beats per minute to 70 beats per minute and the conduction from auricle to ventricle was again prolonged. This was accompanied by a dissociation between auricles and ventricles for a period of 5 seconds (Fig. 2 *F*) after which normal sinus rhythm was again restored (Fig. 2 *G*).

Comment.—The development of partial heart-block for a short period of time after the apparent recovery of normal conduction reproduces in man the same delayed effect of the drug, as is shown by Drury and Szent-Györgyi to be present in the animal.

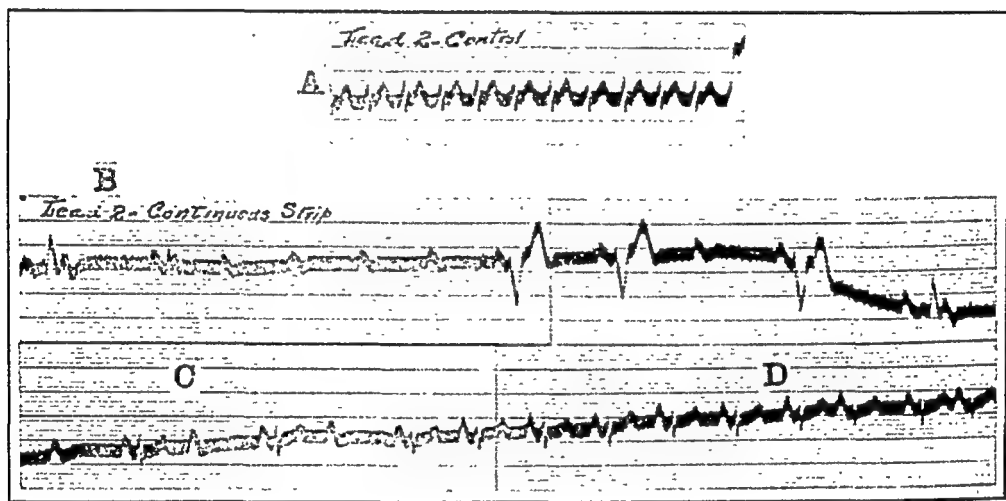


Fig. 3.—The effect of adenosine on paroxysmal tachycardia of auricular origin. Case 1. *A*, Control record, before adenosine; *B*, twelve seconds after adenosine; *C*, twenty seconds after adenosine; *D*, twenty-five seconds after adenosine.

IV. *The Effect of Adenosine on Paroxysmal Tachycardia of Auricular Origin.*—CASE 1.—A male, aged fifty years, who had moderately advanced pulmonary tuberculosis, also suffered from frequently recurring episodes of paroxysmal tachycardia. The paroxysms ended spontaneously one to three days after their onset. Digitalis and quinidine had no effect on the frequency and duration of recurrences of the ectopic rhythm.

Thirty mg. of adenosine were administered intravenously soon after the onset of a recurrence of the ectopic rhythm when the heart action was regular and the rate of beating was 210 per minute (Fig. 3 *A*). Ten seconds after the administration of the drug, the patient complained of giddiness and faintness which lasted for a few seconds. The pulse slowed after 10 seconds (Fig. 3 *B*), then became imperceptible for about 3 seconds, reappeared beating at a slow rate and then the rate gradually increased until it reached the pre-injection rate of 210 beats per minute.

The electrocardiogram shows a slowing of the auricular rate, coming on ten seconds after the injection, followed by complete dissociation between auricles and ventricles for 8 seconds (Fig. 3 *B*). At the same time as the auricular rate increased,

the complete auriculoventricular block changed to partial (2:1) auriculoventricular block (Fig. 3 C). After 25 seconds normal conduction was restored, the heart beating at 150 per minute (Fig. 3 D).

Comment.—In a patient with auricular tachycardia the heart rate was temporarily reduced from 210 to 150 beats per minute after the administration of 35 mg. of adenosine. The coincidental increase in the auricular rate and decrease in the auriculoventricular block is due to the decrease in the effect of the drug as its effect is dissipated on the heart.

CASE 2.—Male, aged forty years, with hypertension, had several seizures of paroxysmal tachycardia which disappeared on one occasion following the application of pressure over the right carotid artery and on the other occasions ended spontaneously. Digitalis had not ended the ectopic rhythm on one trial when a larger dose of the drug was given.

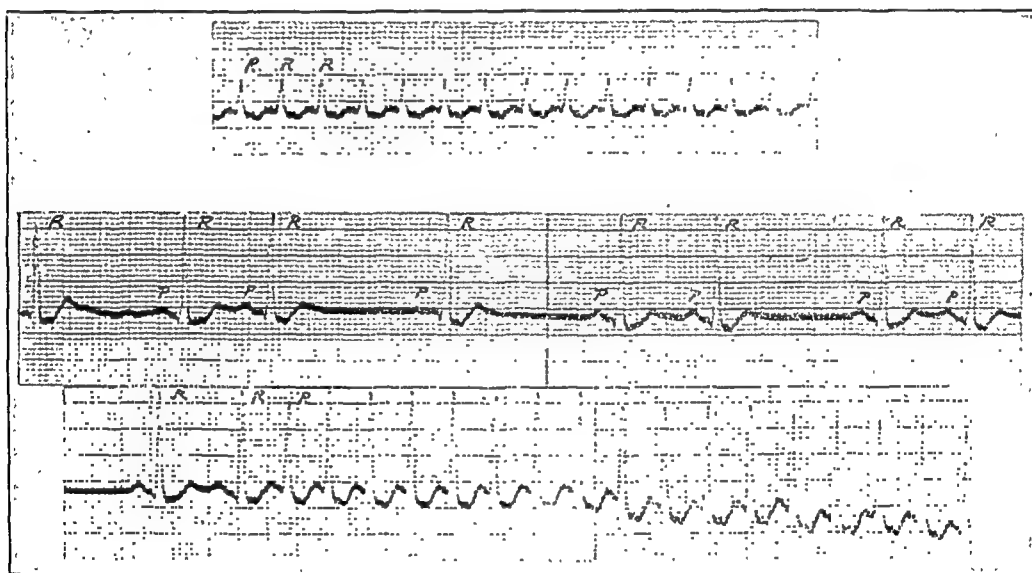


Fig. 4.—The effect of adenosine on paroxysmal tachycardia of auricular origin. Case 2.

Thirty-five mg. of adenosine were administered intravenously soon after the onset of a paroxysm of tachycardia. Although there were pulse pauses of 2-3 seconds' duration, the patient did not complain of any of the subjective effects of the drug.

The electrocardiogram shows a marked depression of the sinus node with periods of standstill of both the auricles and ventricles of one to two seconds. There is no dissociation between auricles and ventricles. The pre-injection heart rate is restored after about 40 seconds (Fig. 4).

V. *The Effect of Adenosine on Tachycardia of Supraventricular Origin.*—In a female, aged fifteen years, with rheumatic carditis, 25 mg. of adenosine were given shortly after the onset of nodal tachycardia. There were no clinical or electrocardiographic changes noted to follow the administration of the drug.

Comment.—Drury and Szent-Gyorgyi have shown experimentally that adenosine has no direct action on the ventricles in animals. It is therefore not surprising that the drug did not have any action in this case.

SUMMARY AND CONCLUSIONS

1. Adenosine was administered intravenously in doses varying from 25 to 45 mg. in eight patients who developed paroxysmal tachycardia while under observation at the hospital.
2. In paroxysmal auricular flutter and in paroxysmal auricular fibrillation, the drug increased the grade of auriculoventricular block for from 40 to 60 seconds. The abnormal rhythm was not abolished.
3. In paroxysmal tachycardia of auricular origin the drug temporarily abolished the ectopic rhythm in one case, and was ineffective in restoring sinus rhythm in a second case.
4. In paroxysmal tachycardia of supraventricular origin there was no effect on the rate or rhythm of the heart.
5. Ventricular standstill for periods of 1-9.2 seconds followed the administration of the drug in the cases with abnormal rhythms of auricular origin. During these periods the patients experienced giddiness, faintness, and precordial pain. The symptoms disappeared with the return of ventricular contractions.
6. In man, adenosine is of doubtful therapeutic value in paroxysmal tachycardia of auricular origin and of no therapeutic value in the other ectopic rhythms which we have studied.

REFERENCES

1. Drury, A. N., and Szent-Gyorgyi, A.: The Physiological Activity of Adenine Compounds With Especial Reference to Their Action Upon the Mammalian Heart, *J. Physiol.* 68: 213, 1929.
2. Bennett, D. W., and Drury, A. N.: Further Observations Relating to the Physiological Activity of Adenine Compounds, *J. Physiol.* 72: 288, 1931.
3. Drury, A. N.: Nucleic Acid Derivatives and the Heart Beat, *J. Physiol.* 74: 147, 1932.
4. Honey, R. M., Ritchie, W. T., and Thomson, W. A. R.: Action of Adenosine Upon the Human Heart, *Quart. J. M.* 23: 485, 1930.

ELECTROCARDIOGRAPHIC STUDY DURING A PAROXYSM OF ANGINA PECTORIS*

G. R. BROW, M.D., AND DELAVAN V. HOLMAN, M.D.
MONTREAL, CANADA

FROM animal experimental work, as yet unpublished, we have concluded that electrocardiographic changes characteristic of those encountered in angina pectoris can be produced by anoxemia. We have by general anoxemia and by transient coronary constriction altered the terminal deflections and affected the normal paths of intracardiac conduction. When adequate oxygenation was restored, the curves returned to normal. Our results agree with those of Kountz and Gruber.¹

Recently we have had the opportunity to take tracings of a patient during an anginal attack. The alterations in the terminal deflections were identical with those we produced experimentally in animals and they were transitory. Within two minutes after the anginal seizure the record was essentially normal. It is our feeling that these alterations were due to anoxemia.²

CASE REPORT

The patient walked into the electrocardiographic laboratory on January 6, 1933, to have the routine tracing made. The three standard leads were taken (Fig. 1). The rhythm was regular, the rate was 90, and the A-V conduction time was normal. In Lead II the T-waves were flattened; they were negative in Lead III. Lead III also showed deepened Q-waves. Slurring of the QRS complexes occurred in all leads.

While the electrodes were still attached he spontaneously developed a paroxysm of substernal pain, typical in all respects of those he had been suffering. A tracing taken at this time (Fig. 2) showed: regular rhythm, rate 75, and normal A-V conduction time. The S-T intervals in Leads II and III had become elevated and in Lead I had become depressed.

Two minutes later, when the attack had spontaneously subsided, a third tracing (Fig. 3) showed: regular rhythm, rate 83, and normal A-V conduction time. The Q-wave in Lead II was deepened. Lead II was the only one recorded.

Thanks to Dr. Joseph Kaufmann, who had referred this patient, we were able to obtain tracings on April 29, 1933. They showed (Fig. 4) regular rhythm, a rate of 75, and normal A-V conduction time. The T-waves were diphasic in Lead II, and negative in Lead III. The Q-waves were deepened in Leads II and III, and there was slurring of the QRS complexes in all leads.

The patient, M. F., a business man, sixty-one and one-half years of age, was referred by Dr. Kaufmann because of chest pain. Prior to 1928, he had enjoyed

*From the University Clinic, Department of Medicine, McGill University and Royal Victoria Hospital, Montreal.

good health. At this time he began to suffer from what was thought to be cardiospasm in spite of the negative findings in x-ray films of the gastrointestinal tract.

Substernal pain first appeared on the evening of January 1, 1933. While walking in the bitter cold he was seized twice with attacks of severe cramplike pain beneath the lower sternum. With each paroxysm he had to stop and rest until it ceased. The pain did not radiate.

The next day and for succeeding days thereafter, the pain recurred on the average of four to five times a day as he went about his usual business. During this time the character of the paroxysms remained constant. It was five days after the onset of the angina that we obtained tracings.

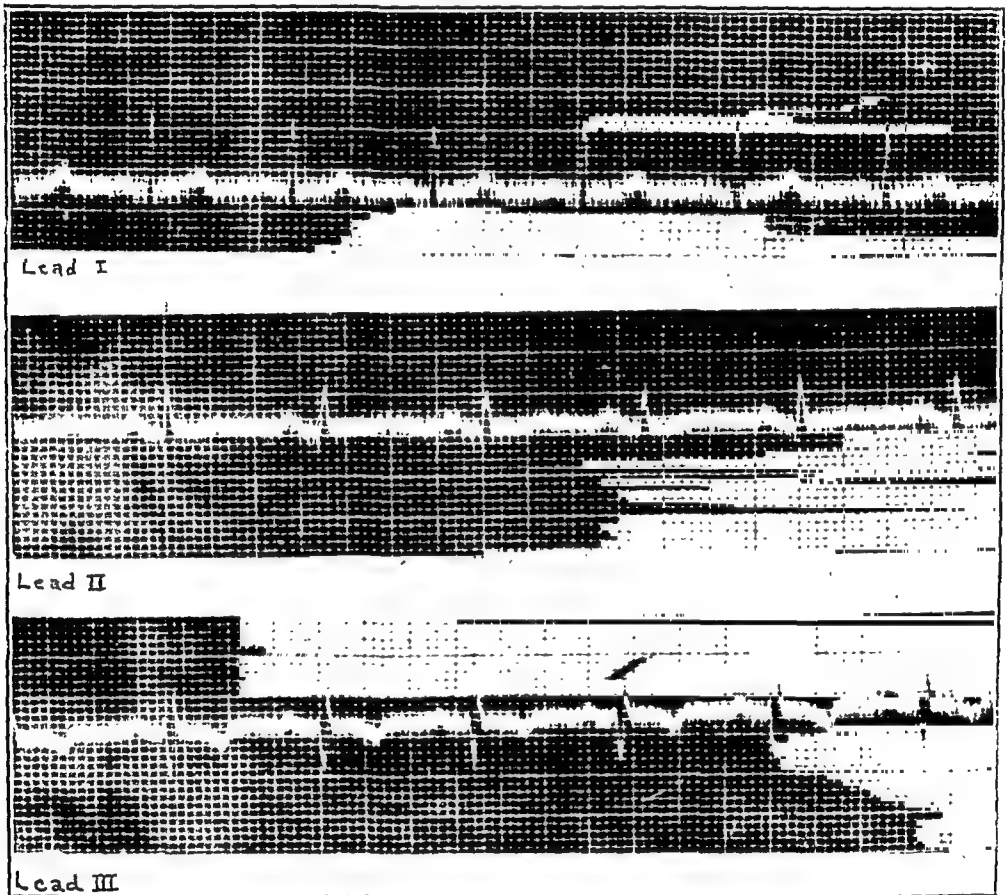


Fig. 1.—Electrocardiogram, three standard leads, taken from patient, M.F., January 6, 1933, just prior to an attack of angina pectoris. Regular rhythm, rate 90, normal A-V conduction time, flattened T-waves in Lead II, negative T-waves Lead III, deepened Q-waves Lead III, slurring of QRS complexes.

From January 6 to January 12, although he rested at home, the attacks continued, coming usually after meals or when he had gotten up to go to the bathroom. On January 13 he was free from pain, and, after four days' further rest, he returned to work. Since this time he has carried out his usual activities with but minor modifications. There have been occasional periods when he has had a sense of mild substernal constriction from overexercise, but there have been no further severe seizures of pain.

He stated that he had never had shortness of breath, headaches, cough or swelling of the ankles and feet. He slept on one pillow. He estimated that he was six pounds under his usual weight.

On April 29, the area of relative cardiac dullness extended from the third left rib downward, bounded by the right sternal border and running 13.5 cm. to the left of the midsternal line when horizontal, and 12 cm. from the same point when erect. There was no widening of the mediastinal dullness in the second interspaces.

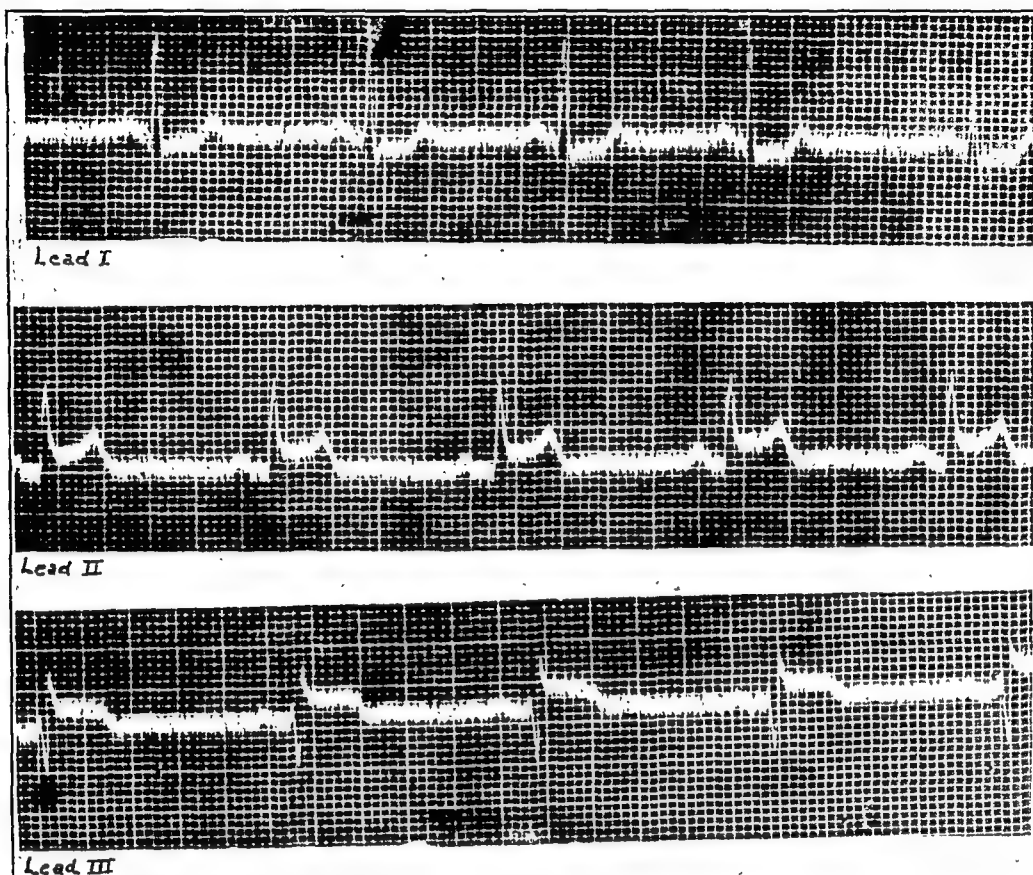


Fig. 2.—Tracings taken of the same patient on the same day, during the height of one of his characteristic seizures of substernal pain. Observe the coronary T-wave type of deviations and compare with the tracing of Fig. 1 and Fig. 3 taken a few minutes before and after the paroxysm. Regular rhythm, rate 75, normal A-V conduction time, elevation of "S-T" intervals in Leads II and III with depressed S-T in Lead I.

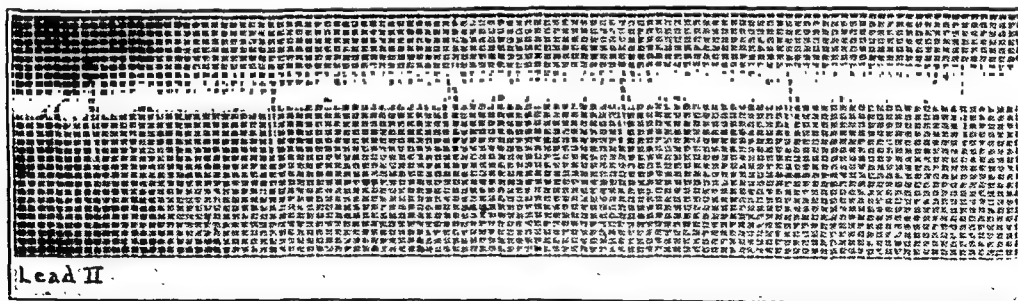


Fig. 3.—Lead II taken less than two minutes after the seizure. Regular rhythm, rate 83, normal A-V conduction—deepened Q-waves in Lead II.

The heart sounds were somewhat distant but were clearly heard. They were less audible at the apex than at the base. The aortic second sound was somewhat louder than the first sound which was associated with a faint blowing systolic murmur. The radial pulses were equal and were of good volume and tension. The heart rate was 74. The systolic blood pressure was 132 mm.; the diastolic 65. There

was no evidence of venous pressure elevation. The vessel walls were moderately thickened. There was no definite arcus senilis.

X-ray films of the heart taken at six feet showed the greatest transverse diameter was 17 cm.; the greatest oblique diameter 17.5 cm. The transverse chest diameter was 29 cm. The greatest transverse diameter of the aorta was 6.5 cm. From the x-ray plates, the enlargement of the heart was greatest to the left of the midsternal line.

There was nothing of note in the remainder of the patient's history or examination. The cranial nerves, deep and superficial reflexes showed nothing unusual. The specific gravity of the urine was 1.018. There was a trace of glucose, no albumin, and nothing abnormal microscopically. The Wassermann reaction was negative.

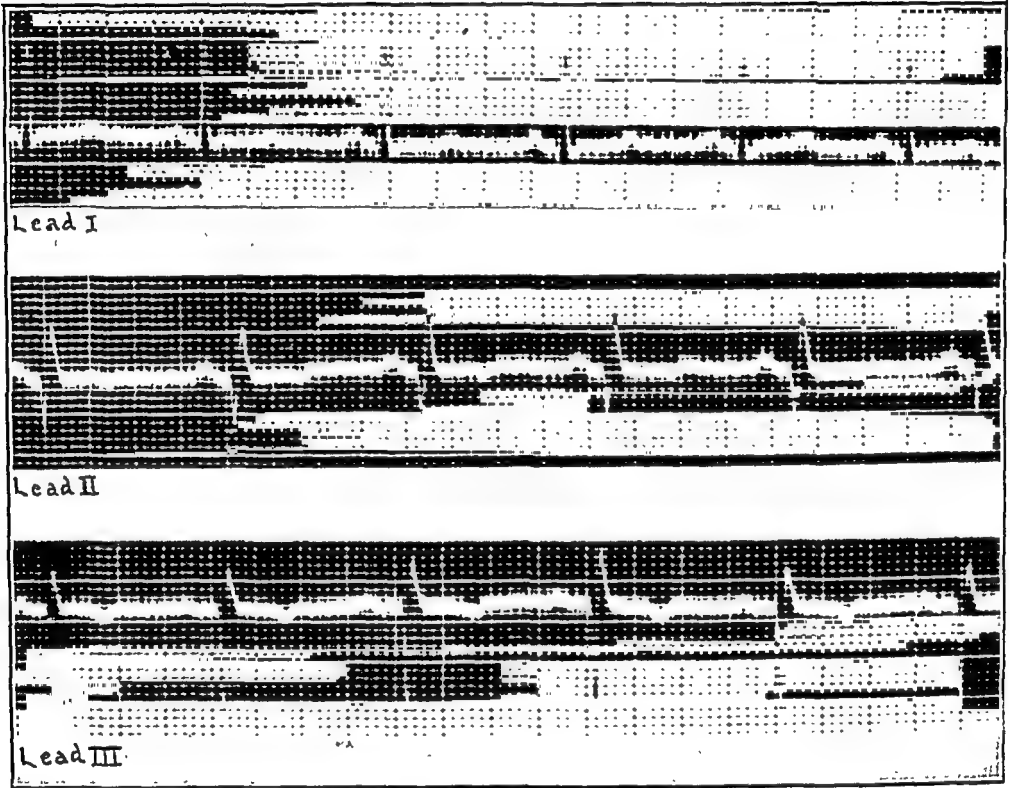


Fig. 4.—Tracings taken April 29, 1933, nearly four months later. Regular rhythm, rate 75, normal A-V conduction time, diphasic T-waves Lead II, negative T-waves Lead III, deepened Q-waves Leads II and III, slurring of QRS complexes.

COMMENT

From the clinical standpoint this patient had moderate peripheral and coronary arteriosclerosis. The heart was somewhat enlarged. The anginal attack which we observed and during which we obtained tracings could not have been due to coronary thrombosis, though the record (Fig. 2) is typical of this condition. Transitory changes of this type must be the result of alterations in the coronary circulation which have caused temporary anoxemia of the myocardium.

We interpret the differences between the curves in Fig. 1 and those of Fig. 2 as evidence of a relatively rapid advance in coronary disease. Whether there had ever been an infarction cannot be proved. The

patient suffered a minimum of fifty severe seizures, and he cannot be persuaded that any one was different from the others. The increased deepening appearing in the Q-waves of Leads II and III is a notable feature in the light of recent work.³

The fact that alterations occurring during the attack (Fig. 2) are not secondary to changes in the QRS complexes is important.⁴

We regret that only Lead II was taken on recovery from the seizure (Fig. 3), but, since some of the most marked changes were present in this axis, we think it should be allowed to stand as evidence of recovery. We feel that records taken a few minutes later would have shown a complete reversion to those in Fig. 1.

DISCUSSION

Electrocardiograms taken during seizures of angina pectoris, that have been described in the literature, fall into three groups: those which show primary deviations in the terminal deflections only,^{5, 6, 7, 8, 9, 10} those which show the bizarre deviations of intracardiac conduction block in one of the bundle branches,^{11, 12} or in the bundle itself,¹³ and lastly those which showed no deviations at all. All three of these groups also appear with coronary thrombosis. In fact, we have concluded that there is only one constant differential point and that is the length of time the changes persist. In coronary thrombosis they last for days but tend to return toward normal in weeks or months; in angina pectoris the return takes only a few minutes. Our case, for example, had recovered in less than two minutes.

A second classification of published cases can be made into two groups: those which were recorded during spontaneous seizures, and those in whom seizures were artificially produced by unusual exercise. We feel that there may be good reason for studying the two groups separately. An entirely different mechanism may be operating in each to produce the attack—possibly a coronary vasospasm in the first group producing localized areas of ischemia, while in the second group a total relative myocardial ischemia is produced by the exercise requirements as they exceed the capacity of the disease-limited coronary circulation. At any rate, cases which showed the most marked deviations in the S-T intervals and in the T-waves, as well as the cases of conduction abnormalities, were all in the spontaneous group. The other group was by far the larger because of the large single series of thirty cases reported by Wood and Wolferth.⁹ What deviations occurred in the artificially precipitated seizures not only were less acute in appearance but it happened that the cases which showed no deviations whatever all fell into this group.

We are reporting our case because it adds another record to the very small group of spontaneous attacks; because it has no predecessor in the literature that we have been able to locate showing the

classical coronary T-wave changes during an attack similar in conformation to those seen in acute myocardial infarction; because it illustrates forcibly the one electrocardiographic differential point between coronary thrombosis and angina pectoris, the fleeting duration; and, lastly, because it apparently reproduces in the human heart what has been seen experimentally in animal hearts, and in this way provides a connecting link in the evidence of the rôle that anoxemia plays in the pathogenesis of angina pectoris.

SUMMARY

1. The electrocardiographic changes in this patient during an attack of angina pectoris were characteristic of those often seen in acute myocardial infarction. After two minutes the curve had returned essentially to normal. The changes, we believe, were due to anoxemia of the cardiac muscle not involving the conduction paths.

2. We have been unable to find a similar case in the literature.

3. The changes are typical of those we have obtained in animal experiments with cardiac anoxemia; similar in conformation and as transitory.

REFERENCES

1. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxaemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
2. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, *Arch. Int. Med.* 41: 760, 1928.
3. Fenichel, Nathan M., and Kugell, Victor H.: The Large Q-wave of the Electrocardiogram. A Correlation With Pathological Observations, *AM. HEART J.* 7: 235, 1931.
4. Wilson, Frank N., Macleod, A. G., and Barker, Paul S.: "T" Deflection of the Electrocardiograph, *Tr. A. Am. Physicians* 46: 29, 1931.
5. Clerc, A.: Anomalies Electrocardiographiques au Cours de l'Obliteration Coronarienne, *La Presse Med.* 35: 499, 1927.
6. Feil, Harold, and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
7. Parkinson, John, and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, *Lancet* 1: 15, 1931.
8. Levy, J. R.: Valeur Semiologique des Alterations du Complex Ventriculaire Electrique dans les Syndromes Angineux, *Arch. d. Mal du Coeur* 22: 523, 1929.
9. Wood, F. C., and Wolferth, Charles C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Occlusion, *Arch. Int. Med.* 47: 339, 1931.
10. Hall, Donald: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, *Lancet* 1: 1254, 1932.
11. Bousfield, Guy: Angina Pectoris; Changes in Electrocardiogram During Paroxysm, *Lancet* 2: 457, 1918.
12. Arillaga, M. F. C.: Signification Prognostique de l'Electrocardiogramme dans les Insuffisance Cardiaques, *Bull. et mém. Soc. méd. d. hôp. de Par.* 32: November 13, 1924.
13. Gallavardin, L., and Rougier, Mlle. Z.: Accés d'Angine de Poitrine avec Hypotension Arterielle Extreme et Accidents Nerveux Syncopaux et Epileptiformes, *Paris méd.* 69: 15, 1928.

Department of Clinical Reports

CORONARY OCCLUSION DUE TO METASTASES FROM CARCINOMA OF THE BREAST*

REPORT OF A CASE COMING TO NECROPSY FIVE YEARS AFTER RADICAL MASTECTOMY

T. A. PEPPARD, M.D., AND L. M. LARSON, M.D.
MINNEAPOLIS, MINN.

REPORT OF CASE

THE patient was a female seventy-five years of age who was first seen January 8, 1929. Her health in the past had been unusually good except for the fact that she had had a carcinoma of the right breast removed by radical resection in 1924, but since then frequent examinations had given no direct evidence of recurrence or extension of the malignancy. Her complaints when first seen were a dependent edema which had been present for a year or so, and a gradually increasing dyspnea, especially on exertion, during the last few weeks.

On examination she was found to be slightly underweight. Her blood pressure in millimeters of mercury was 130 systolic and 74 diastolic, there was no adenopathy palpable, and the scar of the previous mastectomy contained no nodules or indurated areas. There was a firm mass over the midportion of the sternum at the level of the third interspace which was attached to the skin as well as to the underlying tissues. The heart was not enlarged, its rhythm was regular, the rate was 90 beats per minute, and on auscultation no murmurs were heard. Examination of the lungs gave negative results. The liver could be palpated about 3 cm. below the costal margin, and on pressure it was found to be rather tender. There was a mild edema of both legs and ankles.

Laboratory Findings.—The urine showed slight traces of albumin along with varying numbers of pus cells in the urinary sediment. The concentration of the hemoglobin of the blood by the Dare method was 87 per cent, the red cells numbered 5 million, and the leucocytes 7,400 per cubic millimeter of blood. The electrocardiographic tracing showed inversion of the T-wave in the first lead but not in Leads II and III. An occasional extrasystole interrupted an otherwise normal rhythm.

Clinical Course.—The patient was afebrile at all times. On January 24, 1929, and again on February 6 the patient had an attack of severe dyspnea, cyanosis, and weakness, but recovered fairly well after rest and stimulation. The use of digitalis, euphyllin, and theophyllin produced no discernible improvement, and on February 11, the patient died suddenly after a little exertion.

Autopsy.—The body was that of a fairly well-developed and well-nourished female 161 cm. in length and weighing 140 pounds (63.6 kilos). There was a small amount of edema of the feet and ankles, extending about halfway to the knees. There was a scar over the right thorax extending toward the axilla, resulting from the previous radical amputation of the breast. This scar was soft and presented no evidence of recurrence of the malignant process. Over the midsternum at the

*Presented before the Minnesota Heart Society, April, 1929.

level of the third interspace there was a subcutaneous nodule measuring 3 cm. in diameter and quite firm to palpation. This was removed for microscopic study. Examination of the contents of the abdominal cavity gave essentially negative results.

Both pleural cavities contained a quantity of clear, straw-colored fluid, that on the right measuring about 1500 c.c. and on the left 500 c.c. No adhesions were present between the pleural surfaces, and there were no nodules to be found. The pericardial sac was filled with about 800 c.c. of a similar type of fluid. The heart weighed 300 grams and was grossly normal in appearance. Examination of the course of the coronary arteries revealed an unusual finding. The left coronary especially, but also the right, was marked by a pearly white, raised, hard, infiltrating tissue which was almost cartilaginous to palpation, and which extended in variable degrees throughout the length of both arteries down to the small branches. The lumen of these arteries was not completely occluded, but in several areas there were arteriosclerotic patches which practically obstructed the flow of blood. No infarction of the heart muscle could be made out, although the entire myocardium was definitely softened. There were a few arteriosclerotic patches throughout the aorta. Several lymph nodes of the mediastinum were enlarged, and their cut surfaces revealed a dense pearly white, cartilaginous substance identical to that surrounding the coronary arteries, and likewise identical to that found on section of the skin nodule over the sternum. The remainder of the autopsy was without relevant findings. The head and neck were not examined.

Sections for microscopic study were taken from a number of areas along the course of the coronary arteries, and these showed infiltration of the epicardium about the vessel with adenocarcinomatous tissue which extended in several places a short distance into the myocardium, but this was only to a slight degree. The vessel wall itself was not involved in the process, but its lumen was markedly compressed, especially in areas thickened by arteriosclerotic patches. Microscopically the mediastinal nodes and the subcutaneous mass overlying the sternum showed the same adenocarcinomatous structure.

COMMENT

Undoubtedly in this case death was caused by an unusual sequence of events which terminated in occlusion of the coronary arteries. Late metastases from the adenocarcinoma of the breast, which had been removed by radical resection five years previously, appeared in a very unexpected location, namely, in the epicardium surrounding the coronary arteries. The mechanism of the localization of the metastases in this particular place is obscure, although unquestionably the blood stream was the medium through which the transfer of malignant cells took place. While in this person a certain amount of arteriosclerotic thickening could be expected due to her age, yet it probably would have caused few symptoms. However, with the added insult of gradual obstruction of the arterial supply of blood to the heart from the carcinomatous tissue, symptoms and signs of cardiac failure became more and more prominent until death supervened.

Metastatic tumors of the heart, of various types, while they are comparatively rare, have been reported from time to time, but none has been found which corresponds to the type of lesion described in this case.

PAROXYSMAL COMPLETE AURICULO-VENTRICULAR HEART-BLOCK

A CASE REPORT

ADOLPH SACHS, M.D., AND RAYMOND L. TRAYNOR, M.C.
OMAHA, NEB.

WE ARE reporting this case of complete A-V heart-block with Adams-Stokes syndrome because of the following unusual features: (1) The block occurred in paroxysms, the conduction time between attacks being normal. (2) During the presence of the abnormal mechanism the ventricular rhythm was grossly irregular and the ventricular complexes were aberrant and of several different forms. (3) After a period of several months, during which time the patient developed an acute streptococcic sore throat followed by an empyema, the attacks ceased and have not recurred after a period of over two years.

CASE HISTORY

H. B., a single, white laborer, aged forty-three years, was seen first on February 20, 1931, in consultation with Dr. R. L. Sands, who had been called because of a fainting spell accompanied by a convulsion. At the time of our examination the patient had recovered; the cardiac rhythm was regular, the pulse 80 per minute.

During the preceding month the patient had experienced repeated peculiar spells, which began with pounding of the heart, followed shortly by "hot flashes," dizziness, ringing in the ears, weakness, and profuse sweats. On several occasions, during the more prolonged attacks, he had lost consciousness and had been told by his relatives that he had had convulsions. At the first warning of an impending attack he would lie or sit down and as a consequence he had never fallen during an attack. The attacks came without apparent cause and occurred irregularly. On some days he had repeated short seizures and then would go for several days to a week without any trouble.

The family history was irrelevant. He denied all past illness except an occasional sore throat and a severe leg infection several years ago. He was well developed and nourished. The tonsils were infected *grade two*. The lungs were negative. The apex-beat was just within the midclavicular line; the area of cardiac dullness was not increased. A harsh systolic murmur replaced the first sound at the apex and was transmitted into the axilla. Systolic blood pressure was 130, diastolic 80. The palpable peripheral arteries were not sclerotic. Pressure over the vagi did not influence the heart rate.

A seven-foot x-ray film (Fig. 1), taken several days later, showed a heart shadow of normal size and contour.

An electrocardiogram (Fig. 2) revealed a normal rhythm and a P-R interval of 0.18 seconds.

The patient remained symptom-free until March 1, when he again became unconscious and had convulsions. When seen one hour later, he was conscious but

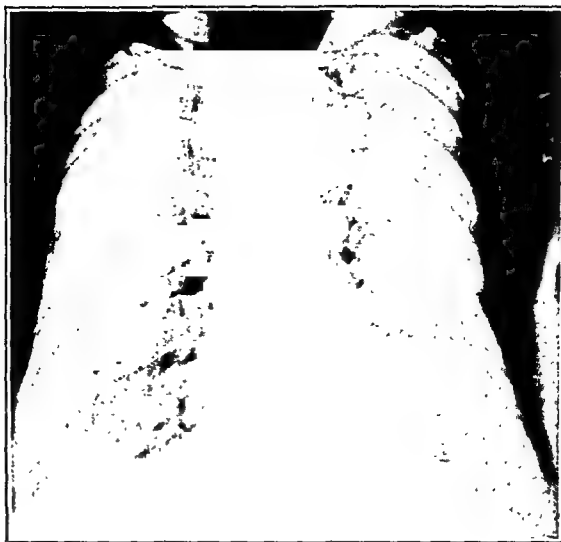


Fig. 1.—A seven-foot film of chest taken on Feb. 23, 1931.

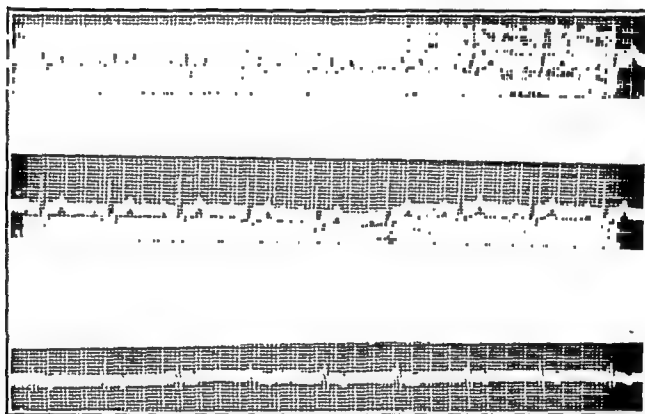


Fig. 2.—Electrocardiogram taken on Feb. 23, 1931. Normal sinus rhythm. P-R interval is 0.10 seconds.

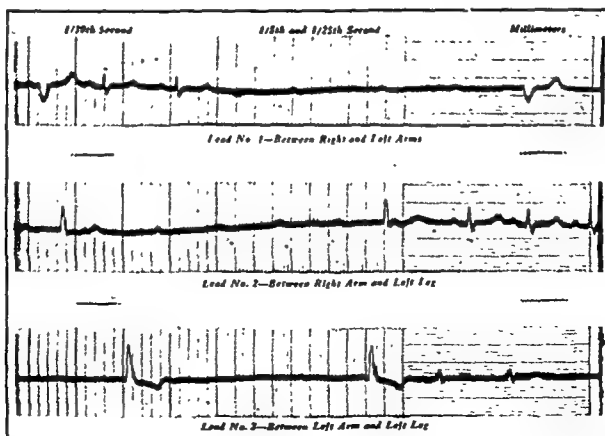


Fig. 3.—Electrocardiogram taken on March 1, 1931. Complete A-V heart-block. Ventricular complexes are aberrant, of several different forms, and are irregular.

would answer questions only in monosyllables. He was pale and frightened. There was no dyspnea. The radial pulse was slow and irregular. On auscultation of the precordium one could hear a regularly recurring sound at a rate of 90 per minute due to auricular contraction; the ventricular contractions, accompanied by a systolic murmur, were slow and extremely irregular. During one quarter-minute period the ventricles would contract once, in the succeeding similar period, there would be four or five beats. The average ventricular rate was 19 per minute. An electrocardiogram (Fig. 3) was obtained. During the night, atropine, caffeine, and adrenalin were given with no change in the condition. The next day a normal rhythm was resumed.

On March 5, the patient was sent to the hospital for observation. For a period of ten days the rhythm was normal; the pulse ranged from 68 to 88. A two-hour

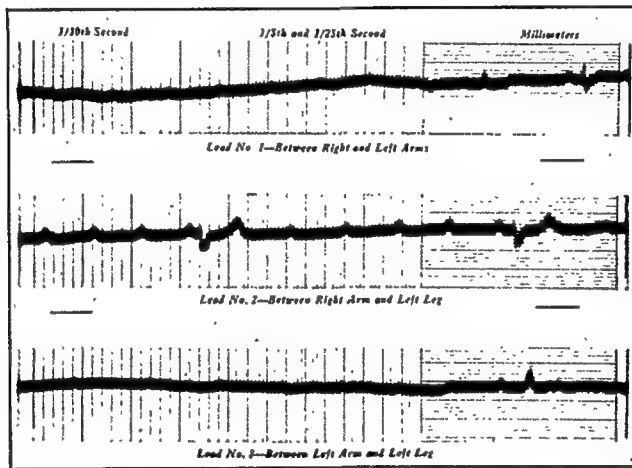


Fig. 4.—Electrocardiogram taken during one of the paroxysms occurring while the patient was in the hospital.

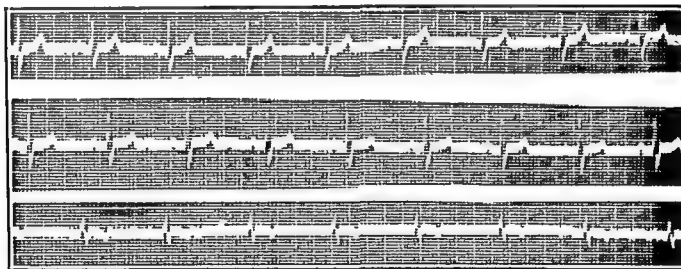


Fig. 5.—Electrocardiogram taken on April 12, 1932. Normal sinus rhythm. P-R interval is 0.16 seconds.

temperature curve showed an absence of fever. A daily leucocyte count was normal. He complained of vague pain in the legs and unlocalized abdominal distress. The Wassermann reaction was negative. Urinalysis was negative.

On March 14, the patient complained suddenly of "hot flashes" and dizziness. His pulse rate dropped to 17 per minute and he became stuporous. He had several epileptiform attacks lasting approximately one minute. The physical findings were, in all respects, similar to those found during the former attack. Atropine sulphate, gr. $\frac{1}{30}$, hypodermically, was without effect. After three hours normal rhythm was restored. Later in the day a similar episode occurred which lasted for only one-half hour.

During the following two weeks the periods of abnormal rhythm recurred daily. The duration of the attacks gradually lengthened until the block was present most

of the time. During the first few days adrenalin would raise the pulse rate and relieve the symptoms but later it seemed to lose its efficacy. Barium chloride and thyroid extract were tried without avail.

On April 2, the patient developed an acute tonsillitis and the temperature rose to 103° F. The pulse rate remained constantly below 40 in spite of the elevated temperature. On April 12, the patient complained of pain in the right axilla, the temperature rose to 104° F., and a pleural rub was heard. On April 24, 800 c.c. of serosanguinous fluid was aspirated from the right pleural sac. The rhythm at this time became normal and remained so. On April 26, a rib was resected and a drainage tube inserted. He experienced considerable respiratory difficulty from the open pneumothorax during the first few days. Convalescence was slow but the patient was discharged without drainage on June 20.

The patient was seen last on April 12, 1933. He had remained entirely symptom-free. His physical findings were essentially the same as when discharged from the hospital. An electrocardiogram (Fig. 5) showed a P-R interval of 0.16 seconds. He had no symptoms of congestive heart failure.

DISCUSSION

The most frequent causes of heart-block are acute infections, notably rheumatic fever and diphtheria, arteriosclerotic heart disease, syphilis, and digitalis intoxication. Overactivity of the vagus often plays an important rôle in precipitating a complete dissociation, as is evidenced by the occasional return of a normal mechanism under the effect of atropine. This is more apt to occur in those cases which result from digitalis. Pardee states that "it is extremely doubtful if it (vagus activity) ever produces more than an accentuation of a condition fundamentally due to disease." That a favorable response to atropine does not exclude organic disease is shown by a case reported by Carter and Dieuade in which a return of a normal rhythm occurred as a result of atropine administration and yet necropsy showed a badly diseased bundle.

It is obvious that a lesion of the bundle of His, whether inflammatory, degenerative, or toxic, may resolve and leave a functionally intact bundle. The not infrequent temporary presence of a block, especially of minor grade, seen during the course of acute infections or after a coronary occlusion demonstrates this fact. The repeated attacks of complete block with a normal conduction time in the interim as seen in this patient are more difficult to explain. We do not feel that they were due to vagus activity alone, especially in view of the fact that atropine was ineffectual and that vagus pressure between the attacks failed to slow the pulse rate.

Carter and Dieuade in attempting to explain a similar case remarked that "there probably exists a large reserve in the conduction capacity of the bundle which may be seriously encroached upon before conduction is measurably impaired; some subtle circulatory or temporary vagal action may result in a failure of the few remaining intact fibers to transmit impulses." In view of the mitral valvulitis in this patient

we feel that he had a rheumatic lesion of the conduction system. A flare-up of this smoldering inflammation would account for the attacks, while its subsidence could explain their cessation.

The idioventricular rhythm which becomes established in complete A-V dissociation is usually slow and regular. Many of the standard textbooks on cardiology fail to mention the fact that the ventricular rhythm in complete block may be irregular. Certainly a gross irregularity is most unusual. Pardee states "that occasionally with complete block the ventricular complexes are aberrant and when this occurs with a regular intersystolic interval it is considered as being due to a variable conduction through one or other bundle branch of an impulse arising in the A-V node. If, however, there is also present a slight coincidental irregularity of ventricular rhythm, both variations are considered as due to a varying site of impulse formation." In the present case, the gross irregularity and change in the form of the QRS is best explained as being due to the formation of impulses at several different sites.

SUMMARY

A case of recurring or paroxysmal complete A-V heart-block is reported. The symptoms associated with the paroxysms constituted the patient's only complaints. He had signs of a mitral valvulitis but had never had any symptoms of congestive heart failure. During the paroxysms the ventricular rhythm was grossly irregular and the ventricular complexes in the electrocardiogram were aberrant and of several different forms. The cause of the block was considered to be a chronic rheumatic myocarditis.

REFERENCES

- Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, New York, Paul B. Hoeber, Inc.
Carter, Ed. P., and Dieuade, F. R.: *Bull. Johns Hopkins Hosp.* 34: 401, 1923.

Department of Reviews and Abstracts

Selected Abstracts

Wiggers, C. J., and Cotton, F. S.: Studies on the Coronary Circulation. I. The Coronary Pressure Pulses and Their Interpretation. *Am. J. Physiol.* 106: 9, 1933.

Pressure pulses were simultaneously recorded from the aorta and either from the central end or from a lateral branch of the anterior descending ramus of the left coronary artery of the dog. Calibrated optical manometers designed and described by one of the authors were used. They had a high figure of merit when tested under conditions of actual use. A technic was developed by which artefacts due to motions of the heart were eliminated.

Such simultaneous records give no indication that the pressure relations or form of the coronary pressure pulse are modified by any factor except the pressure changes in the aorta. The minor changes noted are such as occur in other branches of the aorta. The conclusions of Hochrein and Gros, that in addition heart rate, capacity and elasticity of the aorta, eddies and friction due to an unusually well-developed intima are not supported by these studies. The authors regard these conclusions invalid for (1) comparisons of coronary and carotid pulses do not serve for the study of the problem because the contour and pressure values of the latter differ essentially from those in the aorta, and (2) evidence indicates that the records on which conclusions are based contain many artefacts and hence do not picture the correct form of pressure fluctuations either in the coronary or carotid arteries.

Haney, Hance F., Borman, M. C., and Meek, Walter J.: The Relation Between the Position of Experimental Myocardial Lesions in the Dog and the Changes in the R-S-T Segment of the Electrocardiogram. *Am. J. Physiol.* 106: 64, 1933.

The changes in the level of the R-T and S-T segments of the electrocardiogram were studied following the production of myocardial lesions in the dog. The lesions were produced by means of radon implants. An attempt was made to correlate the position of the lesion with the changes in the level of R-T and S-T.

Lesions on the anterior surface of the left ventricle consistently produced changes of the T_1 type. Lesions on the posterior surface of the left ventricle resulted in changes of the T_2 type in 6 of a total of 7 dogs studied. One showed no change.

Lesions on the anterior surface of the right ventricle resulted in changes of the T_1 type in 5 of 8 dogs studied. The remaining 3 showed no change from the normal. Lesions on the posterior wall of the right ventricle resulted in changes of the T_2 type in 4 dogs, the T_1 type in 2 dogs and no change in 1.

Bowman, James E.: Blood Pressure in the Newborn. *Am. J. Dis. Child.* 46: 949, 1933.

The literature on arterial blood pressure in the newborn is reviewed.

The tension in a group of 100 babies was recorded for the first four days of life, averaging successively 55 systolic, 38 diastolic; 60 systolic, 41 diastolic; 60

systolic, 42 diastolic, and 60 systolic, 44 diastolic. The determinations were made with the Pachon oscillometer, with a 5 by 20 cm. cuff placed about the right leg. In general, the systolic blood pressure is higher in the babies of greater weight at birth, while the diastolic varies little. There was little difference in the blood pressure of 15 babies of the same weight group (from 7 to 8 pounds) born spontaneously.

Interesting observations were noted on comparison of tension before and after drainage of spinal fluid in 4 infants with cerebral hemorrhage.

Bohning, Anne, Jochim, Kenneth, and Katz, Louis N.: The Thebesian Vessels as a Source of Nourishment for the Myocardium. Am. J. Physiol. 106: 183, 1933.

Bismuth was conveyed from the heart chambers into the coronary sinus blood in the beating heart with the coronary circulation isolated from the systemic, in seven out of ten experiments. In two of these experiments, the possibility of any connection between the systemic and the coronary blood by means of extra cardiac anastomoses was excluded by perfusing directly into the coronary arteries.

In preparations of beating hearts with a completely isolated coronary circulation, a suspension of a pure culture of killed bacteria was injected into the superior vena cava. The same bacteria could be demonstrated in the sinusoidal spaces, the capillaries, the small intramural arteries and veins, the superficial branches of the coronary arteries and veins, and also in the blood from the coronary sinus. These experiments, therefore, indicate that the thebesian vessels do form a pathway in the functioning heart by which blood can be conveyed from the heart chambers to the intramural coronary vessels.

Under normal conditions, the amount of blood conveyed by this pathway appears to be comparatively small but in some pathological conditions, where the coronary arteries are occluded, enough blood may find its way into the coronary capillaries to aid appreciably in the nourishment of the heart.

Wright, Irving Sherwood, and Duryee, A. Wilbur: Human Capillaries in Health and in Disease. Arch. Int. Med. 52: 497, 1933.

In this article an endeavor has been made to review the present knowledge concerning human capillaries in health and in many specific diseases. The field is relatively undeveloped, and it is believed that present theories will be discarded in the near future and that many additional pathological processes will be studied from the point of view of the capillaries and circulation. The authors have used an apparatus devised by them and previously described.

In the first section of the paper there is a full discussion of the anatomical appearance and the physiological function of the normal capillaries. In the second section, capillary changes in various disease conditions are described and discussed.

Stainsby, Wendall J., and Nicholls, Edith E.: The Clinical Significance of the Erythrocytic Sedimentation Test in Rheumatoid Arthritis. J. Clin. Investigation 12: 1041, 1933.

The erythrocytic sedimentation test was performed on five hundred and ninety-seven patients with rheumatoid arthritis in order to determine its significance in this disease. The results of the investigation indicate that the corrected sedimentation index is a reliable criterion of the activity or severity of the arthritic process at the time of testing, and that any fundamental change in the clinical condition produces immediate corresponding change in the sedimentation rate. Patients with greater degrees of joint involvement and a longer disease duration

have higher sedimentation rates on the average, than those with less joint involvement and shorter disease duration. Considerable variation occurs, however, in individual cases.

The observation that the average sedimentation rate progressively increases with advancing age periods is of interest. This phenomenon appears to be due primarily to the increasing accumulation of patients with severe arthritis in whom the disease began at some earlier age.

From a study of seasonal variations in the sedimentation rate over a long period, suggestive evidence was deduced that on the average the rate was higher in winter than in summer, while spring and autumn occupied intermediate positions. No relationship was found between the sedimentation rate and the streptococcus agglutination reaction.

With the above-mentioned information at hand, it seems justifiable to discuss the practical importance of this test. In the past, physicians treating arthritis have been greatly handicapped by lack of means for estimating the results of their therapy. The sedimentation test appears to supply this widely felt need, as it is a reliable measuring rod of the activity or severity of the arthritic process. By repeating this test at regular intervals the progress of the patient may be determined. The sedimentation test provides a ready aid for correctly estimating the value of various treatments proposed for rheumatoid arthritis.

Struthers, R. R., and Bacal, H. L.: Determination of the Activity of Rheumatic Infection in Childhood. *Canad. M. A. J.* 29: 470, 1933.

It is concluded after observations on thirty-one cases of rheumatic infection that uncomplicated rheumatic fever shows a high sedimentation rate, usually a leucocytosis of 12,000 to 15,000, fever, approximation of the sleeping and waking pulses during the period of fever, and loss of weight. All these evidences of activity tend to subside with the clinical evidence of subsidence of the infection. Rheumatic fever with carditis shows a sedimentation rate which requires a period of months to return to normal, and hence is probably the most delicate of these tests in the determination of activity of rheumatic infection, except in the presence of congestive failure with edema when it falls rapidly to levels below the normal and is of grave prognostic import.

It was found that chorea without carditis shows no alteration in the total white blood cell count, sedimentation rate, or fever. When the chorea is complicated with carditis even in the absence of fever, it shows the same changes in these criteria as does rheumatic fever with carditis, except the absence of leucocytosis.

Wilkins, Walter E., and Cullen, Glenn E.: Electrolytes in Human Tissue. III. A Comparison of Normal Hearts With Hearts Showing Congestive Heart Failure. *J. Clin. Investigation* 12: 1063, 1933.

The right and left ventricles of 17 human hearts were analyzed for water, phosphorus, sodium, potassium, magnesium, and calcium. Of these hearts, 5 were normal, 4 were from persons who had cardiac disease but who died from other causes, and 8 were from persons who died with congestive heart failure.

The water content of the diseased right ventricle tends to be slightly higher than that of the left ventricle. The water content of both ventricles of hearts from persons who died with congestive heart failure was found to be increased. The normal left ventricle contains more total phosphorus and more potassium than the right. Both ventricles of diseased hearts showed a decrease in total phosphorus and potassium. The normal right ventricle contained more sodium

than the normal left ventricle. Sodium was increased in both ventricles of persons who died with congestive heart failure. Usually the right ventricle contains a slightly higher concentration of calcium than does the left ventricle. No consistent variations were found in the calcium content of the ventricles of persons who died with congestive heart failure. Both the normal and diseased left ventricles were richer in magnesium than the corresponding right ventricles. Both ventricles of the diseased hearts showed a diminution in magnesium.

The sums of the individual bases when calculated in milliequivalents per kilo of tissue water show that the two ventricles do not differ essentially in their content of total base. The potassium-sodium ratio in the normal left ventricle is higher than in the normal right ventricle. Both ventricles of the diseased hearts showed a decrease in this ratio. The phosphorus-potassium ratio was somewhat higher in the right ventricle than in the left. The diseased hearts had nearly the same phosphorus-potassium ratio in both ventricles as did the normal hearts, showing that the former had a proportionate decrease in phosphorus and potassium.

Harrison, William Groce, Jr.: The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea. J. Clin. Investigation 12: 1075, 1933.

A study was made of the cisternal pressure, the lumbar spinal fluid pressure, the systemic venous pressure, the vital capacity, the arterial blood pressure, and the pulse and respiration rates in the recumbent and upright positions in five patients without cardiac disease and in five patients with congestive heart failure.

The arterial blood pressure and pulse rate were usually slightly greater in the sitting than in the prone position, but, in general, the blood pressure and the pulse and respiration rates showed no marked consistent changes with position in either group. The systemic venous and lumbar spinal fluid pressure were greater in the sitting than in the prone position in each subject and were much greater in each position in the patients with congestive heart failure than in the patients without cardiac disease. The vital capacity was greater in the sitting than in the prone position in both groups of cases, and the percentile increase of vital capacity with change in position was greater in the patients with cardiac disease.

The cisternal pressure was much greater in each position in the group with congestive heart failure than in the other group. The cisternal pressure was much less in the upright than in the recumbent posture in each case, and this difference in cisternal pressure between the two positions was much greater in patients with congestive heart failure than in those without cardiac disease. As a result of these observations, it is believed that in addition to the increase in vital capacity, the diminished cisternal pressure is an important factor in producing the relief from dyspnea obtained in the sitting position. The mechanism of this effect is, as yet, unknown.

Seham, Max, and Hilbert, Eunice H.: Muscular Rheumatism in Childhood. Am. J. Dis. Child. 46: 826, 1933.

The results of a study of thirty-five children suffering from what are predominately chronic muscular pains are presented in this paper. No evidence was found to substantiate the old idea that normal growth causes chronic muscular pains. It is believed that the term "growing pains" is a misnomer and should be discarded. Chronic pains in the muscles which can be differentiated from chronic fatigue and definite orthopedic disorders are probably the result of a chronic infection.

Twenty-one per cent of 208 children from eight to fifteen years of age gave histories of having muscular pains over a period of three months or more. The age incidence of these muscular pains was practically the same as that for all other forms of rheumatism. It was no higher during puberty than at any other period.

There was a significant relation between muscular pains and inadequate sleep and fatigue.

Systolic murmurs developed in 30 per cent of the children who had continuous fever and in only 19 per cent of the children who were afebrile. Of these, 11 per cent acquired chronic mitral endocarditis. The average sedimentation rate at the end of one hour for the normal group was 5.9 mm.; for the convalescent rheumatic persons and those in whom the disease was inactive, 10 mm.; for those with muscular rheumatism, 8.7 mm.; and for those with chorea, 11 mm. The average streptococci agglutination titer for the normal group was 1:160 and for the children with muscular rheumatism, 1:1,500. In the normal group, 92 per cent of the titers were below 1:200, whereas, in the abnormal group only 7 per cent were below 1:200.

Hoyle, Clifford: Pituitary Secretion in High Blood Pressure. *Quart. J. Med.* 2: 549, 1933.

It is not possible to detect pituitrin in normal unconcentrated human cerebrospinal fluid obtained by lumbar puncture, even if sufficient be taken to make it probable that it comes from the cerebral cisterns.

Patients with essential hypertension or with hypertension associated with chronic renal insufficiency do not usually show an excess of pituitrin in such cerebrospinal fluid. Pituitrin may be detected occasionally, but even then only minute traces are found. The absence of a significant increase is held to be strong evidence that hyperpostpituitarism is not concerned as an etiological factor in these varieties of hypertension.

Wood, Francis Clark, Bellet, Samuel, McMillan, Thomas M., and Wolferth, Charles C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads. *Arch. Int. Med.* 52: 752, 1933.

Thirty-six cases of acute coronary occlusion are reported in which chest leads as well as limb leads were used in the electrocardiographic study. Three chest leads were used: Lead IV, from the lower precordium to the angle of the left scapula; Lead V, from the lower precordium to the left leg, and Lead VI, from the angle of the left scapula to the left leg.

The exact location of the anterior chest electrode is important in determining the contour of the electrocardiogram. This has not been true in the case of the posterior electrode. The methods used in taking chest leads and the normal findings in Leads IV, V, and VI are discussed.

Certain variations which have been seen in pathological cases without acute cardiac infarction are described. Deviations in the RS-T interval may occur in chest leads in the absence of acute coronary occlusion.

An electrocardiographic analysis of our 36 cases shows that 31 of them tend to fall in one or the other of two groups, termed for convenience Groups A and B.

Group A consists of 19 cases. Examples of this group are shown in charts. Four cases in this group which have come to necropsy have shown occlusion of the left anterior descending coronary artery, with infarction of the anterior surface of the left ventricle, usually including the apex and the anterior half of the interventricular septum.

Group B consists of 12 cases. Examples of this group are shown in charts. The data at hand suggest that these are cases of infarction of the posterior wall of the left ventricle due to occlusion of the right coronary artery.

When chest leads as well as limb leads were used, all but one of the cases of acute coronary occlusion showed electrocardiographic evidence of the lesion during the first few days. The absence of deviations of the RS-T interval in all six leads renders the diagnosis of recent coronary occlusion quite unlikely.

Certain characteristic alterations produced in the QRS complex as a result of coronary occlusion tend to persist. Thus, several months after coronary occlusion has taken place, the findings in the QRS complexes and T-waves may point to the nature of an antecedent attack. There are certain indications that the symptoms of a posterior infarction when compared with those of an anterior one, are often less dramatic and less prolonged; that the immediate prognosis is less grave, and that the subsequent recovery of adequate cardiac function is apt to be more rapid and more complete.

Landis, Eugene M., and Gibbon, John H.: A Simple Method of Producing Vasodilatation in the Lower Extremities. Arch. Int. Med. 52: 785, 1933.

The forearms of patients were immersed in warm water (43° to 45° C.) for thirty-five minutes in order to produce vasodilatation in the lower extremities. This vasodilator response was studied in 24 patients two showed clinical evidence of peripheral vascular disease.

In 7 patients with pain, coldness, or cyanosis of the lower extremities, the temperature of the toes rose to levels above 32° C. This normal response definitely excluded the possibility of obliterative structural disease of the arteries as a cause of the diminished flow of blood in the lower extremities.

Four patients with thromboangiitis obliterans or arteriosclerosis involving the lower extremities showed varying grades of organic occlusion and spasm when tested by this method.

In 8 of the 13 patients who failed to show the normal vasodilator response to warming the forearms, the results were compared with those obtained by some other method of producing vasodilatation, including the intravenous injection of typhoid vaccine, the use of spinal anesthesia, and anesthetization of the posterior tibial nerve. In 7 of the 8 patients the clinical interpretation of the findings by both methods was the same. In 1 patient with arteriosclerosis warming the forearms failed to produce a vasodilator response, whereas anesthetization of the posterior tibial nerve showed that the vessels were capable of limited dilatation.

Three patients with acrocyanosis of the lower extremities showed abnormal vasodilator responses to warming the forearms, though anesthetization of the posterior tibial nerve produced complete, but rather delayed elevations in skin temperature. These findings are discussed with reference to the mechanism of the diminished flow of blood in acrocyanosis.

Warming the forearms in water at a temperature of from 43° to 45° C., for thirty-five minutes is a simple and entirely unobjectionable method of producing vasodilatation in the lower extremities. If the surface temperature of the toes rises above 31.5° C., significant obliterative structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present. With controlled room temperature, the approximate grade of the organic obstruction is indicated by the difference between 31.5° C., and the maximum temperature reached. For absolute certainty in the diagnosis of organic arterial obstruction, the abnormal

vasodilator responses obtained by warming the forearms should be confirmed by some other method of producing peripheral vasodilatation.

Laws, Clarence L., and Levine, Samuel A.: *Clinical Notes on Rheumatic Heart Disease With Special Reference to the Cause of Death*. Am. J. M. Sc. 186: 833, 1933.

One hundred and forty-eight cases of rheumatic heart disease were studied to ascertain the cause of death. It was found that congestive heart failure accounted for only 33.1 per cent of the fatalities, acute rheumatic carditis for 23 per cent, peripheral emboli and thromboses for 11.5 per cent, subacute bacterial endocarditis for 29 per cent, and 3.4 per cent died of miscellaneous cardiovascular accidents, such as angina pectoris or acute pulmonary edema.

The groups of congestive failure and emboli and thromboses were the oldest, subacute bacterial endocarditis a little younger, and acute rheumatic carditis the youngest.

Those that had aortic valvular disease alone were the oldest (52.5 years). The mitral cases came next (42.8 years) and the patients with combination of aortic, mitral, and tricuspid were youngest (30 to 35 years).

There were more than twice as many females as males dying of acute rheumatic carditis, the relation was reversed in the group dying of emboli and thromboses, and the proportion was 3 to 2 on the side of males in the subacute bacterial endocarditis group.

A past history of rheumatic fever or chorea was not found with equal frequency among the various groups. While the authors believe that stenosis of any of the valves is, except in rare instances, of congenital heart disease, practically invariably due to rheumatic infection, the multiform character of the early illness prohibits obtaining a positive past history in many instances. The greater the number of valves involved, the more frequently was a positive past history obtained. This is true for two reasons: such patients are more apt to have had more than one infection and they die at a younger age, so that the early illnesses are not forgotten. This explains why patients with aortic stenosis who die at an old age less frequently have a positive past history.

In speaking of valvular lesions in this review, except for those patients dying of subacute bacterial endocarditis, we mean stenosis to a greater or lesser extent. A striking finding was the great frequency of involvement of the aortic and tricuspid valves. When the tricuspid valve was involved, the mitral was always diseased as well, and frequently the aortic.

Auricular fibrillation was almost invariable in the emboli and thrombi group, very common in those dying of congestive heart failure, much less common in the acute rheumatic carditis group, and practically absent in those who died of subacute bacterial endocarditis. The presence of mitral stenosis is the most common accompaniment of auricular fibrillation, although this irregularity occurs occasionally in patients who have only aortic stenosis.

The average weight of the heart of those dying with congestive failure was 617 gm., of acute rheumatic carditis or emboli and thromboses about 550 gm., and of subacute bacterial endocarditis 449 gm. The average weight of the heart in cases of aortic stenosis was 669 gm., of mitral stenosis 474 gm., and of both 663 gm. When the tricuspid was involved in combination with other valves, the average weight was about 550 gm. The presence of adhesive pericarditis increased the average weight by about 120 gm. The average weight in 43 patients with adhesive pericarditis was 654 gm., and in 62 patients with a normal pericardium was 534 gm.

Pericarditis with or without adhesions was less frequent in the older patients. It was most common in the group with acute rheumatic carditis, fairly frequent in those with congestive heart failure, and very rare with subacute bacterial endocarditis.

Otto, Harold L., Gold, Harry, and Messeloff, Charles R.: *Studies on Digitalis in Ambulatory Patients With Cardiac Disease. V. Further Observations on the Nature of the Cumulation of Digitalis.* Arch. Int. Med. 52: 725, 1933.

The present study was undertaken to ascertain the curve of the cumulation of digitalis in patients with a regular sinus rhythm without heart failure, the criteria being changes in the P-R interval and in the T-wave which may, under these conditions, be ascribed only to a direct action of the drug and which cannot be produced as indirect effects of an improved state of the general circulation.

Many difficulties encountered in the course of the study reduces the number of successful experiments to such an extent that on only 12 of the 75 patients was it possible to carry out observations that were adequate for the purpose of the investigation.

It was possible to demonstrate the following facts:

1. One daily dose of digitalis was insufficient to produce the full effects seen after the continued administration of the drug.
2. With the continued daily administration of digitalis a curve of increasing intensity of effects resulted.
3. After a time, a level was reached beyond which the effects did not increase in intensity.
4. This level was maintained for a length of time sufficient to insure that the dose could not produce greater effects by any criterion of the action of digitalis.
5. A larger dose was capable of producing greater effects, which indicated that the criteria employed were sufficiently sensitive to reveal the presence of more digitalis.

It is believed that the experiments carried out in this study confirm the conclusions of Gold and deGraff, that patients do not excrete a fixed quantity of digitalis daily, but one that varies with the amount present in the body.

Gilchrist, A. Rae: *The Action of Adrenalin in Complete Heart-Block.* Quart. J. Med. 2: 499, 1933.

Twelve cases of complete heart-block have been tested with repeated subcutaneous doses of adrenalin in an attempt to discover the factors which govern the response of the heart to this drug.

After a subcutaneous dose, the drug comes into action with surprising rapidity. Acceleration of auricles and ventricles may occur within two to four minutes of the injection. The amount of ventricular acceleration induced bears a striking relationship to the rate existing immediately before the injection. High initial rates are followed by little or no gain in rate, slow rates by pronounced acceleration. This means that the state of the heart at the time of the drug's administration determines the heart's response.

By plotting the observed increment against the corresponding initial rate, it is found that for a group of 8 cases the reaction approximates to an almost perfect series of decreasing exponentials for increasing ventricular rates.

Within a certain range of dosage, the amount of adrenalin injected makes little or no difference to the ventricular response at a given ventricular rate. The optimum response to 0.5 c.c. adrenalin for various initial rates has been

calculated and compared with the reaction observed after doses of 0.25, 0.75, and 1.0 c.c. in the same subjects. The gain in rate after these doses is to all intents similar to that recorded after 0.5 c.c. This implies that the response of the heart is determined, not by the size of a dose in the usual therapeutic range, but by the rate of the heart existing at the time of the injection. In other words, for a given initial rate 0.25 c.c. of adrenalin will produce as much acceleration as a dose four times that amount.

This phenomenon is discussed in the light of the known laws which govern enzyme action. The independence of the size of the dose and the response recorded, suggests that a surface action is involved and that adrenalin is being adsorbed on some (? enzyme) surface, as an essential condition of the action.

The observation that the initial rate determines the degree of acceleration finds support in blood pressure studies. Lyon has suggested that the reaction to adrenalin obeys Weber's law, in that the amount of elevation in the systolic blood pressure, after uniform doses of adrenalin, depended upon its level at the moment of the injection.

It has not been found possible to demonstrate as close a correlation between the initial auricular rate and its increment after adrenalin as that observed in the case of the ventricles. The auricular response is modified to some extent, particularly in those cases in which the magnitude of the ventricular response is maximum, that is, when the initial ventricular rate is relatively low.

It would appear probable that reflex vagal influences, induced by a marked ventricular reaction, limit the auricular response. The amount of limitation is apparently determined largely by the initial ventricular rate.

The course of the reaction to a subcutaneous dose of adrenalin varies as much in complete block as it does in the normal beating heart. The maximum auricular and ventricular reactions are not necessarily synchronous. As a general rule, the auricles attain to the height of their reaction before the ventricles have completed their acceleration. An increased frequency of both chambers of the heart persists after the blood pressure rise has returned to its preexisting level. No untoward symptoms resulted from the use of the drug. Release from the block was not observed in any of the experiments performed upon these 8 patients.

Reactions differing from those just described were encountered in 4 patients. One of these cases was a man who suffered from intermittent complete block. Tested with adrenalin during complete block, no change in the rhythm occurred but a branch defect changed from one side of the heart to the other. Tested during 2 to 1 rhythm, complete block was induced. The direction of the main ventricular deflection varied according to the presence or absence of conduction through the main stem of the bundle. During half-rhythm the ventricular complex in Lead III was directed downward, whereas during complete dissociation its direction was upward. The fact that this man's heart was unduly susceptible to adrenalin suggests that in cases of intermittent complete heart-block, the temporary failure of conduction, leading to transient complete dissociation, may perhaps be associated with the formation within the body of some subtle and complex chemical substance analogous to adrenalin or adenosine.

Book Review

NOUVELLE MÉTHODE POUR LA DÉTERMINATION DES CHRONAXIES MYOCARDIQUE ET HISIENNE. By Adalbert van Bogaert, Sc.D., M.D., 191 pp. Poitiers. Société Française d'Imprimerie, 1933.

This monograph contains an account of observations on the excitability of the heart as determined by the chronaxie method of Lapicque. The purpose of the study appears to be the identification of certain cardiac disturbances from measurements of the "stimulability" of the heart in a special way that is designated as "longitudinal and transverse chronaxie."

The introduction contains a brief statement of the meaning of chronaxie (i.e., the intensity-duration characteristic of a stimulus) so that the reader unfamiliar with this method may gain an idea of the basic principles of the procedure. The main part of the work is presented under two divisions. The first deals primarily with experiments and arguments to establish the thesis of two distinct chronaxies in the heart (i.e., parts of the cardiac musculature having distinctly different excitabilities) and the second part contains an elaboration of this concept in an attempt to show that in certain disturbances, manifest by changes in the P-R and QRS intervals in the electrocardiogram, there is a prolongation of one of these chronaxie measurements.

The author makes use of the fact that the heart as a functional organ presents two structures histologically and physiologically, and upon this he postulates two chronaxies: one corresponding to the striated cardiac muscle and the other to the His-Tawara system. A large number of experiments are reported, covering a variety of procedures and pertaining to both the cold-blooded and the mammalian heart. From these one gleanes that the basic things in the work probably center in the following considerations: (a) measurements of differences in excitability within the heart can be detected when the plane of the testing electrodes is transversely across the heart at the level of the A-V junction; (b) this chronaxie is two, three, or more times that for any other plane; and (c) this chronaxie measurement is definitely that of the His bundle system.

If one follows the experimental results as given, the fact seems convincing that a difference in chronaxie exists in a certain transverse plane of the heart, but doubt will come to the minds of those familiar with chronaximetry as to the interpretation of a causal relationship between this transverse chronaxie and the specialized tissue of the heart. Moreover, the extension of this line of reasoning to apply practically to the detection of changes in the conducting system from measurements made through the closed thorax, seems to be a generalization that will require additional evidence. Since the changes in the transverse ("His'") chronaxie that are brought about with certain drugs (particularly ephedrine) to stimulate the usual type of disturbances over the conducting system are portrayed to a large extent by characteristic alterations in the electrocardiogram, the reasons for employing the chronaxie method carry less weight.

The monograph includes at the end a fairly complete bibliography and a helpful table of contents. The text contains many illustrations and a large number of concise tabulations which add greatly to the ease of following the argument and denote much care in its preparation.

D. J. E.

LA ANGINA DE PECHO. By Dr. Gregorio N. Martinez, Profesor de Clinica Medica de la Facultad de Cordoba. 278 pp. Buenos Aires, 1933, Humberto Andreetta.

In this volume of 278 pages the author attempts a systematic presentation of the subject of angina pectoris, using the term in its older and more general sense to include cases of coronary closure and cardiac infarction.

Much space is given to the subject of treatment, both medical and surgical, and there are included the condensed protocols of 49 personal cases. The book gives evidence of wide reading and is furnished with a full bibliography.

L. A. C.

ARRITMIAS. By Dr. Antonio Battro. 246 pp. Buenos Aires, 1933, Sebastian de Amorrutu.

This volume, well printed and well illustrated, should be useful to the Spanish-speaking clinician. In addition to a discussion of the different arrhythmias, it includes the usual introductory chapters on general considerations and graphic methods. The author has succeeded in presenting established facts in a clear, concise form, providing a handbook suitable for the student or practitioner.

E. H.

The American Heart Journal

VOL. 9

FEBRUARY, 1934

No. 3

Original Communications

HEART DISEASE FROM THE POINT OF VIEW OF THE PUBLIC HEALTH—1933*†

ALFRED E. COHN, M.D., AND CLAIRE LINGG, M.A.
NEW YORK, N. Y.

WHETHER the death rate from "heart disease" is increasing is still the subject of active debate. A report was made dealing with several aspects of this problem in 1926.¹ Since then, the number has seemed to be mounting² though doubt concerning the correctness of this belief has been expressed by responsible public health officers.³ The present report was undertaken to continue the study begun in 1926.

Certain preliminary decisions have necessarily been taken. The curves published in 1926 described the course of events in the original ten registration states and the District of Columbia. It seemed wise therefore to continue to confine this study to this area. These states, the registration area of 1900, comprised the states of New England, New York, New Jersey, Indiana, and Michigan. This plan has two advantages: first, the record is the longest available in the United States; and second, this area presents, within not too wide limits, similarity of climate. There is a third advantage; the area is large. Inferences drawn from occurrences here are less likely to be unduly sensitive to modifying local influences. Local influences may indeed issue in consequences of considerable importance. Evidence is, as a matter of fact, becoming available which suggests that the course of rheumatic fever and its lesions may actually differ with latitude and longitude, with humidity, with the quality of sunlight. In short, the natural history of a disease elsewhere need not be identical with that in the registration area of 1900. Conversely, a description of an area as a whole need not be applicable to a subdivision of that area, to New York City for example. The area may be regarded as the

*From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Heart Committee, New York Tuberculosis and Health Association, New York.

†Based on a report made to The American Public Health Association, Washington. D. C., October 24, 1932.

"hinterland" of the cities. What occurs in any section of it may have legitimate geographical interest, but is less significant when the subject of study is the course of a disease. Continuing to confine this study to the same states has another advantage. It suggests the advisability of making parallel studies in other regions differing in climate, light, altitude. Differences may be found not only in the course of rheumatic fever but in the behavior of other cardiac affections as well. Comparison may be expected to deepen insight into the nature of these various processes.

In the summary of the report of 1926 these paragraphs appear:

3. It is borne out by study of the curves which relate infectious and heart diseases, that the two have moved in opposite directions. The curve which represents the former has been falling, while that of the latter has risen. But the relation is not quite simple, for neither curve travels a smooth course. It is, however, possible to notice that at certain points, changes in the direction of both curves have taken place. It is furthermore noticeable that there occurred a delay in the increased rise of the curve from heart disease for a number of years after that of the infectious diseases began to fall. That this period is seventeen years may have a meaning but it is not an obvious one and no insistence is placed upon it. That there should be a delay like this is easily comprehended; if individuals fail to die of infection, they will die in some other manner, and of affections which develop or are incident to life at later ages.

4. That the data which have been accumulated support this view seems clear, for the curves all show that the increased rate of death from the heart diseases involves persons over age forty. Under this age, the rates, as these curves show have actually fallen. Additional confirmation of this view resides in the fact that the rate increases with each decade.

These opinions form the starting point of this further study. The curves* carried formerly to 1923 (Figs. 1 and 2) now include the facts to the year 1930. They show that the direction of the slopes of the curves remains unchanged. The inference that a relation exists between decrease in deaths from infectious diseases, and increase in those from other causes in later decades, especially from the heart diseases, seems still to be justified. Since 100 per cent of the population dies, the outstanding question becomes "When?" To discover this, curves of the death rates at each decade (the specific death rates) were constructed (Fig. 2). In the heart diseases they show that *before* the age of forty the rates had been falling steadily since the year 1900; and that *after* the age of forty, they rose, and did so the higher, the older the age group. Recently, since 1920, in the older decades, they show a tendency to flatten. In the infectious diseases they show that the rates were falling and were doing so in *every* decade. This is a matter of importance to which it will be necessary later to return.

*We are indebted to Miss Whittemore and the other members of the staff of the Research Committee of the New York Heart Committee for their aid in constructing these curves. We are under great obligation to the Bureau of the Census, and to Dr. Murphy for transcribing the figures necessarily used in making the curves. We wish especially to express our indebtedness to him for his courtesy and cooperation.

Under these circumstances the deduction seemed simple and justified that freedom from infectious diseases, known to have taken place on a large scale, has resulted naturally in increase in the number and

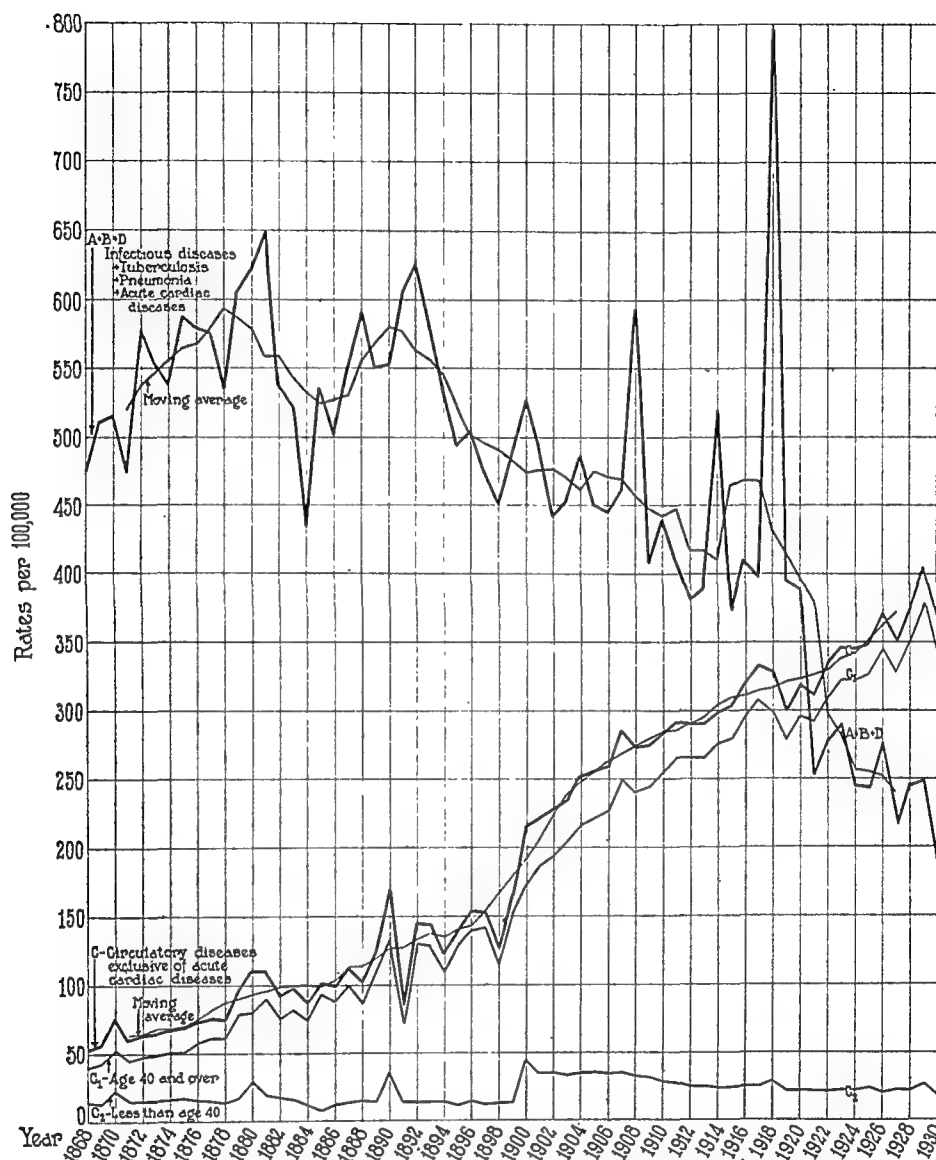


Fig. 1.—These curves exhibit the mortality rates per 100,000 of various diseases in the First Ten Registration States plus the District of Columbia from 1868-1930. Curve A+B+D describes the course of events when infectious diseases, tuberculosis, the pneumonias and acute cardiac diseases are added; Curve C, that in circulatory diseases, exclusive of acute cardiac diseases; Curve C₁ includes of Curve C, only those age forty and over; C₂ includes of Curve C, only those less than age forty.

Diseases grouped as follows:

A—(Infectious diseases)
Typhoid fever
Measles
Scarlet fever
Whooping cough
Diphtheria
Influenza
Mumps
Dysentery
Acute poliomyelitis

Meningococcal meningitis
Malaria
Cholera nostras
B—Tuberculosis
Pneumonia
Bronchopneumonia
C—(Circulatory diseases exclusive of acute cardiac diseases)
Apoplexy
Angina pectoris

Other diseases of the heart (including endocarditis)
Diseases of the arteries
Other diseases of the circulatory system.
D—(Acute cardiac diseases)
Pericarditis
Acute endocarditis and myocarditis

States included: Connecticut, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island, Vermont, and District of Columbia.

tained injuries *in earlier years*, from scarlet fever or from diphtheria for example, of such a nature as to predispose them to disease of the heart, the number and rate of deaths from heart disease among them might, presumably, be greater than among those who had not experienced these illnesses. This suggestion has actually been made.⁴ The correctness of this supposition is, at the present however, not open to analysis; there are no suitable reports of morbidity. Until these, so seriously wanted, are supplied, neither this nor other similar suggestions can be tested. Whether it is important to make this analysis will appear on further consideration.

The second qualification arises from the possibility that the death rate in a decade of age is modified by changes taking place *in that decade itself*. This possibility can be studied. If, for example, of 100 persons aged sixty, 10 persons formerly died of pneumonia but do so no longer, dying now of a heart disease instead, the number who die of a heart disease is increased by the number no longer dying of pneumonia. The saving from infectious diseases has in fact been more than great enough in the sixth and tenth decades themselves to account for the increase in the number of deaths per 100,000 from the heart diseases, but in the seventh, eighth, and ninth, they were not, although the savings in these decades attained considerable dimensions (Table I). Other causes must account for the increase.

To do so, search may be instituted in another direction. The inquiry shifts now to consideration of "fashion" in diagnosis.³ Changes

TABLE I

CIRCULATORY AND RENAL DISEASES					
AGE	(A B C D E)*				INCREASE
	1900		1930		
40-49	261.8		250.7		-11.1
50-59	598.1		721.3		+123.2
60-69	1389.9		1962.3		+572.4
70-79	3478.9		5048.5		+1569.6
80-89	8895.0		11908.5		+3013.5
90+	21053.7		22090.4		+1036.7
INFECTIOUS DISEASES†					
AGE	(1) 1900*	(2) 1930	(3) DECREASE	(4)	(4) - (3)
				INCREASE IN A B C D E	
40-49	447.7	183.8	-263.9	-11.1	
50-59	555.2	231.6	-323.6	+123.2	-200.4
60-69	876.7	345.5	-531.2	+572.4	+41.3
70-79	1589.6	625.9	-963.7	+1569.6	+605.9
80-89	2970.0	1315.8	-1654.2	+3013.5	+1359.3
90+	4188.5	2203.4	-1985.1	+1036.7	-948.4

*These letters designate briefly the rubrics shown in Fig. 3.

†The infectious diseases are those designated in Table III.

in the number of deaths entered in a diagnostic rubric are known to take place. The reasons for these changes are numerous. R. L. Levy² has shown that in the Presbyterian Hospital in New York City the number of times the diagnosis, thrombosis of coronary arteries, for example, was entered increased sharply after the publication of papers on the subject by J. B. Herrick. Attention was, it seems, focussed sharply on a special form of illness and resulted in greater diagnostic acumen. Reports on this subject to the Bureaux of Vital Statistics in the registration area obviously can influence the form of the curves

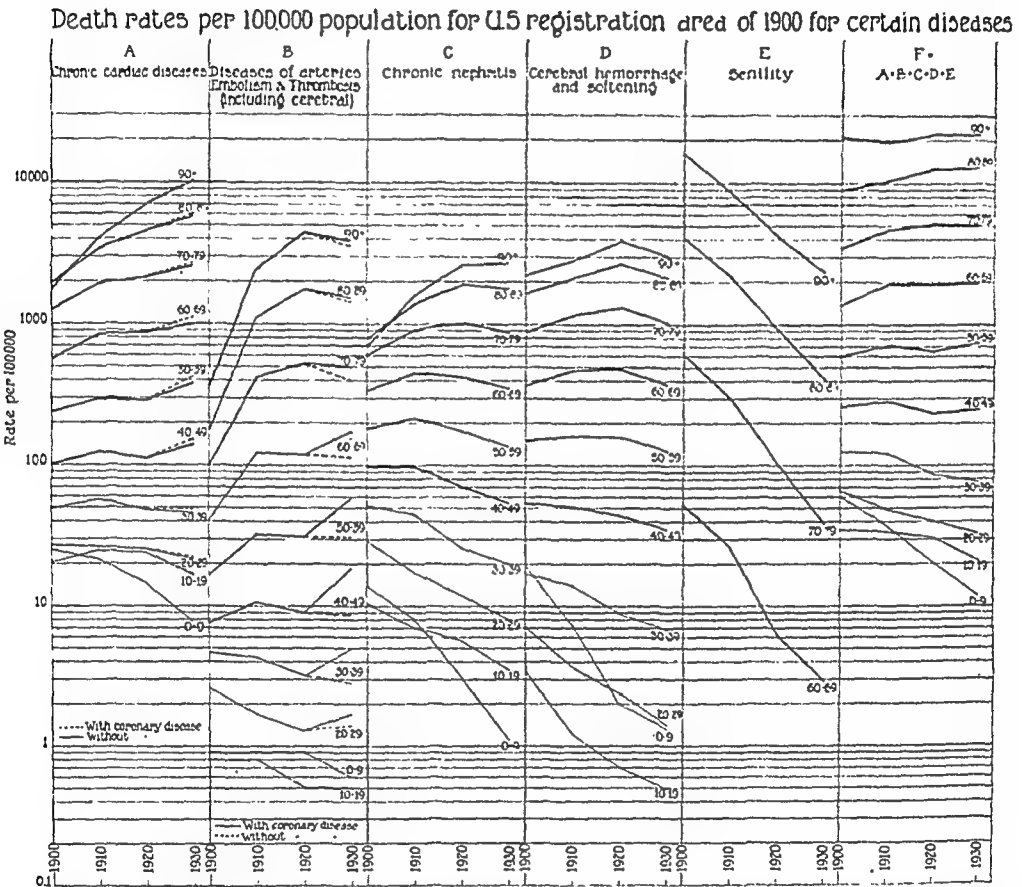


Fig. 3.—A to F. These curves describe the course of the rate of mortality at each decade of life under five separate rubrics for the four years, 1900, 1910, 1920, 1930. A exhibits the situation in chronic cardiac diseases; B, that in diseases of the arteries; C, in chronic nephritis; D, in cerebral hemorrhage and softening of the brain; E, in senility. F gives the rates when these five classes of disease are added. Table II indicates which code numbers are used and the equivalent code numbers in succeeding editions of the International List of Causes of Death.

(Fig. 3, A and B). And again increase in knowledge or further consideration of the problem of classification may account for the violent changes which have taken place under the head of senility (Fig. 3, E).*

Similar changes may have occurred in the categories, "chronic cardiac diseases," "diseases of the arteries," "chronic nephritis," "cere-

*These statements ignore, as they may, difficulties connected with double entries in registration.

bral hemorrhage and softening of the brain," and "senility." Conceivably, for reasons not wholly apparent, cases entered under one may, at another time, be entered under another heading. Scrutiny of all the categories employed in the International List of Causes of Death has singled out those which have just been named as the ones especially liable to change of this sort. Each of them has in fact undergone alteration (Fig. 3, A, B, C, D, E). If, instead of making the effort to understand the behavior of each class separately, this group of chronic ailments is regarded as a whole, as a unit, a better insight into what has been the course of events may be secured. When this is done it becomes obvious that the death rate in each decade of life be-

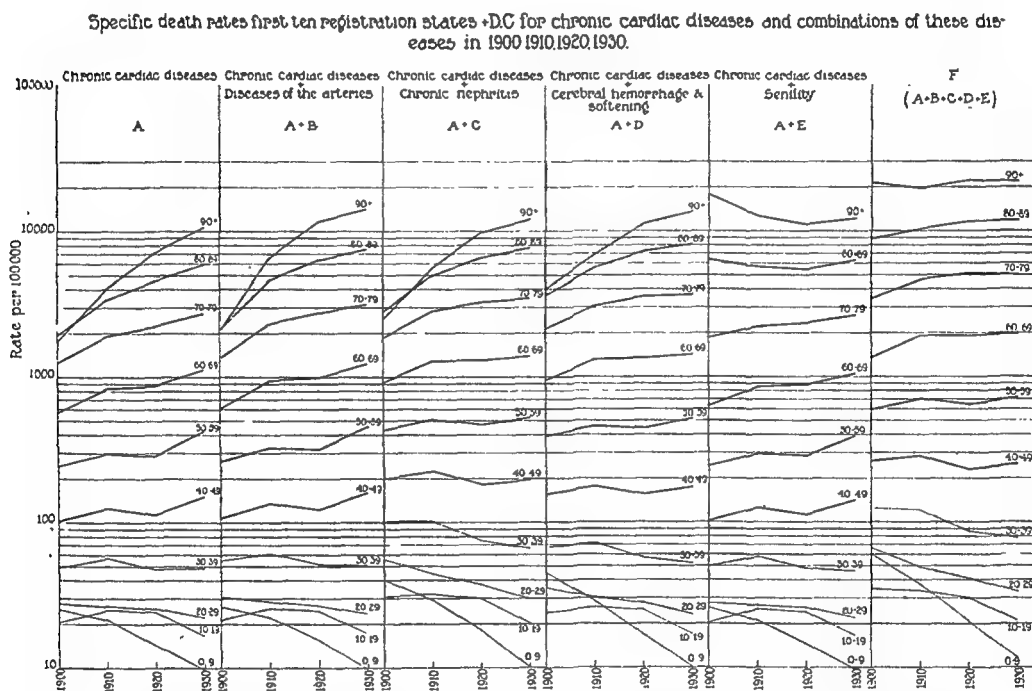


Fig. 4.—These curves describe the course of the death rate at each decade of life in the rubric "chronic cardiac diseases" and combinations of these rates with other selected rates:

- A. The rates for chronic cardiac diseases are given separately and are identical with those in Fig. 3, A.
- A+B. The rates for chronic cardiac diseases are combined with those of diseases of the arteries (Fig. 3, A+B).
- A+C. The rates for chronic cardiac diseases are combined with those of chronic nephritis (Fig. 3, A+C).
- A+D. The rates for chronic cardiac diseases are combined with those of cerebral hemorrhage and softening (Fig. 3, A+D).
- A+E. The rates for chronic cardiac diseases are combined with those of senility (Fig. 3, A+E).
- F. The rates given for these five classes of disease are added. This set of curves is identical with those in Fig. 3, F.

ginning with the fifth has remained much more nearly constant; the curves have become much more nearly flat (Fig. 3, F). This observation may be described in another way; when the effort to arrange the cases under appropriate but arbitrary rubrics is ignored, and a more general scheme of classification is adopted, descriptive nevertheless of the group, the members within which are reasonably closely related,

a sharp increase has obviously not occurred. Even if to the class "chronic cardiac diseases" (Fig. 4, A) that of "senility" (Fig. 3, E) alone is added, the resulting curve (Fig. 4, A+E) presents a form in striking contrast to that of the two component curves. But whether the group is regarded as a whole (Fig. 4, F) or merely from the point of view of a combination of "chronic cardiac diseases" and "senility" (Fig. 4, A+E) or of any other combination of which A is one element, the result (Fig. 4) shows that a rise has taken place in the decades beginning with the fifth (except A+C and F), though taken as a whole (Fig. 4, F) the rise is distinctly smaller than is the case when it occurs in any one, singly.

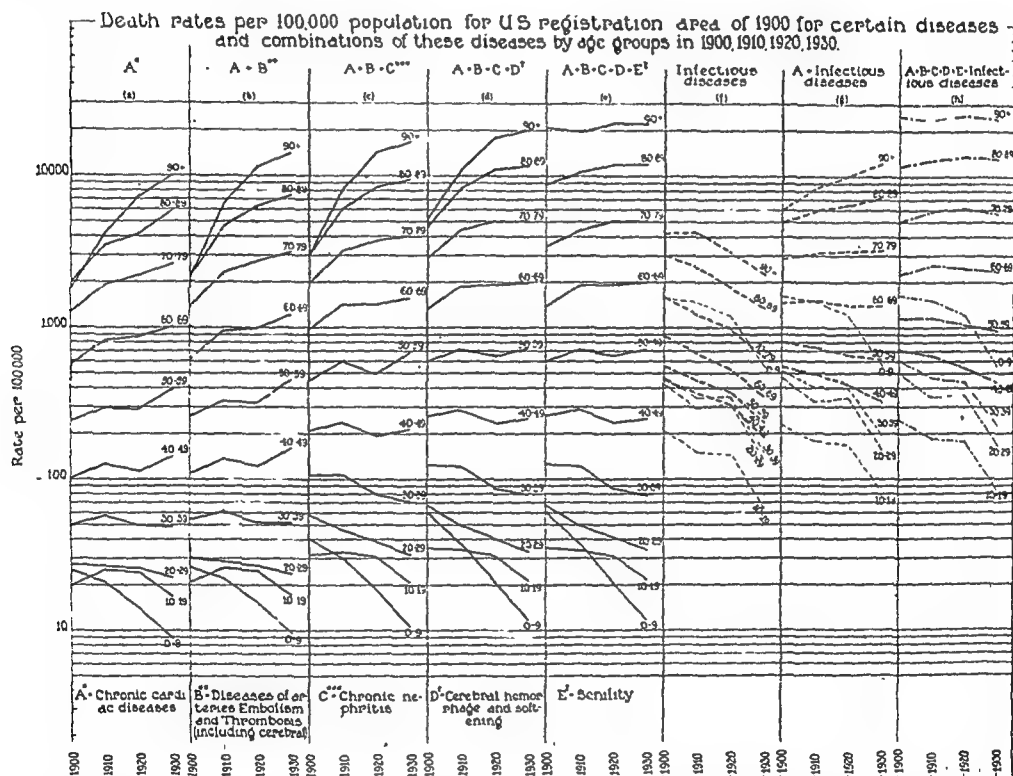
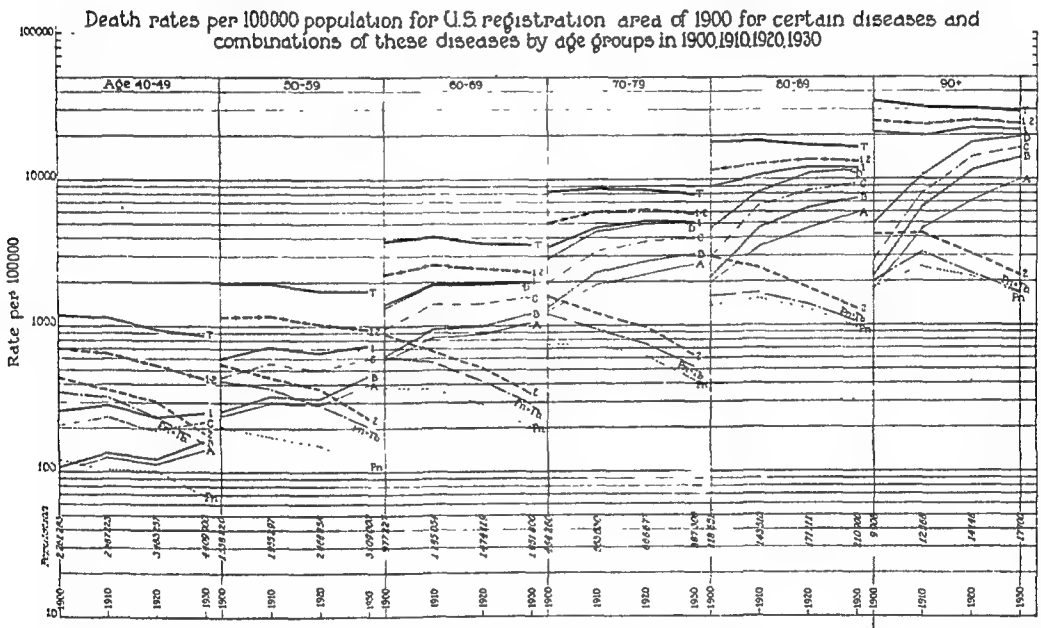


Fig. 5.—These curves describe the course of the death rates at each decade of life in the rubric "chronic cardiac diseases"; of those in the infectious diseases, and of combinations of these with other selected rates.

- The rates for chronic cardiac diseases are given separately and are identical with those in Fig. 3, A.
- The rates for chronic cardiac diseases are combined with those of diseases of the arteries (Fig. 3, A+B).
- The rates for chronic cardiac diseases and diseases of the arteries are combined with those of chronic nephritis (Fig. 3, A+B+C).
- The rates for chronic cardiac diseases, diseases of the arteries, and chronic nephritis are combined with those of cerebral hemorrhage and softening (Fig. 3, A+B+C+D).
- The rates for chronic cardiac diseases, diseases of the arteries, chronic nephritis, cerebral hemorrhage, and softening are combined with those of senility (Fig. 3, A+B+C+D+E). This set of curves is identical with those in Fig. 3, F.
- These curves describe the course of the death rates at each decade of life in the infectious diseases. Table III indicates which items are used and the equivalent code numbers in succeeding editions of the International List of Causes of Death.
- The rates of chronic cardiac diseases (a) and infectious diseases (f) are combined.
- The rates in (e) and infectious diseases (f) are combined.

If the course of events in the infectious diseases is now considered again, the meaning of the fall in the death rate compared with that of the circulatory group becomes apparent (Fig. 5). It is in these two great groups, the infectious and circulatory diseases (inclusive of chronic nephritis) in which by far the majority of all deaths is included. The two together should approximate the total death rate. The addition does in fact correspond with this assumption; the interval between the sum (Fig. 6, Curve 1-2) and the total rate (Fig. 6, Curve T) is relatively small and has become steadily smaller with time. But the result of the addition presents a new problem. In the fifth, sixth, and tenth decades, as the curves (Figs. 6 and 7 in comparison with Fig. 3, Curve F and Table I) show, the decreases in infectious diseases are greater than the increases in the circulatory group.



In Figs. 6 and 7 the method of presentation is changed. In these figures the data are arranged not according to diseases, but according to age. In each column are given data concerning the circulatory group and the infectious group.

Fig. 6.—Curve A describes the course of the death rates in chronic cardiac diseases.

Curve B adds to Curve A the death rates in diseases of the arteries.

Curve C adds to Curve B the death rates in chronic nephritis.

Curve C adds to Curve B and represents therefore the death rates in cerebral hemorrhage and softening and represents therefore the death rates of this entire circulatory group.

Curve D beginning in the seventh decade adds to Curve C the death rates in cerebral hemorrhage and softening.

Curve 1 beginning with the seventh decade, adds to Curve D the death rates in senility and represents therefore the death rates of this entire circulatory group.

Curve Pn gives the death rates from the pneumonias.

Curve Pn+Tb adds to Curve Pn the death rates from tuberculosis.

Curve 2 adds to Curve Pn+Tb the death rates of *all* the other infectious diseases. For the code numbers used of the infectious diseases, see Table III.

Curve 1+2 is the sum of Curve 1 and Curve 2.

Curve T adds to Curve 1.2 the death rates of *all* the other causes of death and describes therefore the total death rate.

The slope of the curves is downward (difference between 1900 and 1930). The meaning of this seems to be that the effect of saving from infectious diseases continues to result in a positive balance (decrease

TABLE II

CODE NUMBERS OF CHRONIC CARDIAC DISEASES, DISEASES OF THE BLOOD VESSELS, AND OF THE KIDNEYS IN SUCCEEDING EDITIONS OF THE MANUAL OF THE INTERNATIONAL LIST OF CAUSES OF DEATH

YEAR	CHRONIC CARDIAC DISEASES	CHRONIC NEPHRITIS	DISEASES OF THE ARTERIES EMBOLISM AND THROMBOSIS (INCLUDING CEREBRAL)	CEREBRAL HEMORRHAGE AND CEREBRAL SOFTENING	SENILITY
1900 (List published 1902)	79. Organic diseases of heart 80. Angina pectoris	120. Bright's disease	81. Diseases of the arteries, atheroma, aneurysm, etc. 82. Embolism and thrombosis	64. Congestion and hemorrhage of brain 65. Softening of the brain	154. Senile debility
1910 (1909 revision used)	79. Organic diseases of heart 80. Angina pectoris	120. Bright's disease	81. Diseases of the arteries, atheroma, aneurysm, etc. 82. Embolism and thrombosis	64. Congestion and hemorrhage of brain 65. Softening of the brain	154. Senility
1920 (1909 revision used)	79. Organic diseases of heart 80. Angina pectoris	120. Bright's disease	81. Diseases of the arteries, atheroma, aneurysm, etc. 82. Embolism and thrombosis	64. Congestion and hemorrhage of brain 65. Softening of the brain	154. Senility
1920 (revision used for Fig. 8)	89. Angina pectoris 90. Other diseases of heart	129. Chronic nephritis (including unspecified, 10 yr. and over)	74b. Cerebral embolism and thrombosis 91. Diseases of arteries a. Aneurysm b. Arteriosclerosis c. Other diseases of arteries 92. Embolism and thrombosis (not cerebral)	74a. Cerebral hemorrhage 83. Softening of the brain	164. Senility

TABLE II—CONT'D

YEAR	CHRONIC CARDIAC DISEASES	CHRONIC NEPHRITIS	DISEASES OF THE ARTERIES EMBOLISM AND THROMBOSIS (INCLUDING CEREBRAL)	CEREBRAL HEMOR- RHAGE AND CEREBRAL SOFTENING	SENILITY
1930 (1929 re- vision used)	<p>92. Chronic endocarditis, valvular diseases</p> <p>a. Endo. specified as chronic, and other valv. diseases</p> <p>b. Endo. unspecified (45 yr. and over)</p> <p>93. Diseases of the myocardium</p> <p>c. Chronic myocarditis and myocardial degeneration</p> <p>d. Unspecified</p> <p>94. Diseases of coronary arteries and angina pectoris</p> <p>a. Angina pectoris</p> <p>(b. Diseases of coronary arteries)</p> <p>95. Other diseases of the heart</p> <p>a. Functional diseases of the heart</p> <p>b. Other and unspecified</p>	<p>131. Chronic nephritis</p> <p>132. Nephritis, unspecified (10 yr. and over)</p>	<p>82b. Cerebral embolism and thrombosis</p> <p>(94b. Diseases of coronary arteries)</p> <p>96. Aneurysm (except of heart)</p> <p>97. Arteriosclerosis (diseases of coronary arteries excepted)</p> <p>99. Other diseases of the arteries</p>	<p>82a. Cerebral hemorrhage</p> <p>82c. Softening of the brain</p>	162. Senility

TABLE III
CODE NUMBERS OF INFECTIOUS DISEASES IN SUCCEEDING EDITIONS OF THE MANUAL OF THE INTERNATIONAL LIST OF CAUSES OF DEATH

YEAR	TUBERCU- LOSIS	PNEU- MONIA	OTHER INFECTIOUS DISEASES										MALARIA	CHOLERA NOSTRAS
			TYPHOID FEVER	MEASLES	SCARLET FEVER	WHOOP- ING COUGH	DIPH- THERIA	INFLU- ENZA	MUMPS	DYSEN- TERY	ACUTE POLIOMYELITIS	MENINGO- COCCAL, MENIN- GITIS		
1900 (List publ. 1902)	(26 to 35) incl.	92, 93	1	6	7	8	9	10	Not listed as separate title	14	63 ("Other dis- cases of spinal cord") Ac. polio. <i>not</i> listed as spec. title	61	4	13
1910 (Re- vision of 1909 used)	(28 to 35) incl.	91, 92	1	6	7	8	9	10	Not listed as separate title	14	63 ("Other dis- cases of spinal cord") Ac. polio. <i>is</i> listed as sep. title	61 ---	4	13
1920 (Re- vision of 1909 used)	(28 to 35) incl.	91, 92	1	6	7	8	9	10	Not listed as separate title	14	63 ("Other dis- cases of spinal cord") Ac. polio. <i>is</i> listed as sep. title	61	4	13
1930 (Re- vision of 1929 used)	(23 to 32) incl.	107, 108, 109	1, 2	7	8	9	10	11	Listed under .44 (c) one of several titles, .. not included	13	16	18	38	12

in the Curve 1-2, which is reflected in the total rate) until the seventh decade.* Not until the influence of this movement in the infectious diseases comes to an end, can stability in the slopes of all the curves be expected. Completion of the process will, it seems, result in ever higher populations in the decades beyond those in which the saving occurs. Barring the influence of other affections, such as cancer, rises in the circulatory group must consequently occur until these also in turn become stable. This is the result which seems, as a matter of fact, to be taking place. Beginning with the sixth decade, an increase in the circulatory group is apparent until 1910 or 1920; then greater stability begins to occur (Fig. 6).

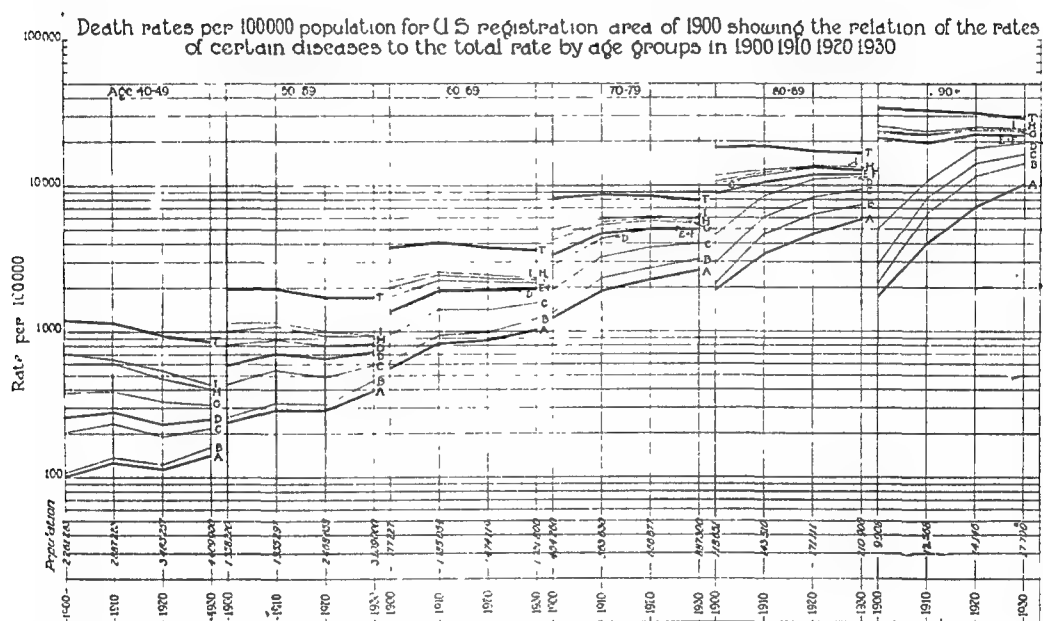


Fig. 7.—This is similar to Fig. 6 in that curves A, B, C, D are identical. In the fifth and sixth decades, D (senility) is omitted. The rates of the infectious diseases are given not independently but as additions to the preceding:

In the fifth and sixth decades D and, beginning with the seventh decade, E (= Fig. 3, F) represent the death rates of the entire circulatory group. Curve G adds to Curve D (fifth and sixth decades) or E (= Fig. 3, F) beginning with the seventh decade, the rates in pneumonias.

Curve H adds to Curve G the rates in tuberculosis.

Curve I adds to Curve H the rates in the other infectious diseases.

Curve T adds to Curve I the rates in *all* the other causes of death and describes therefore the total death rate. It is identical with Curve T in Fig. 6.

As a result of these reflections certain inferences can, it appears, be drawn:

- A. 1.—In the later decades the death rate has increased distinctly in A (chronic cardiac diseases) and B (diseases of the arteries); less in the three highest decades in C (chronic nephritis) and D (cerebral hemorrhage and softening of the brain); and has fallen sharply in E (senility) (Fig. 3).

*It seems unnecessary to attribute to savings (from scarlet fever, for example) in *early life*, an influence which does not become operative, even in a small way, until the seventh decade.

2.—If the circulatory and renal group is studied as a whole (Fig 3, F) with the view to ignoring fashions in diagnoses, reflecting in part as these do increase in knowledge, especially of an anatomical nature, increases in the death rate are observable beginning with the sixth decade but the increases are slight in comparison with what have been regarded as the facts, based on a consideration of "chronic cardiac diseases" alone, and have tended to mount relatively little since 1910.

B. The rates in infectious diseases have fallen in every decade (Fig. 5).

C. 1.—If the rates in the two groups (circulatory and infectious) are added (Figs. 5, 6, and 7), the death rate tends to attain equilibrium.

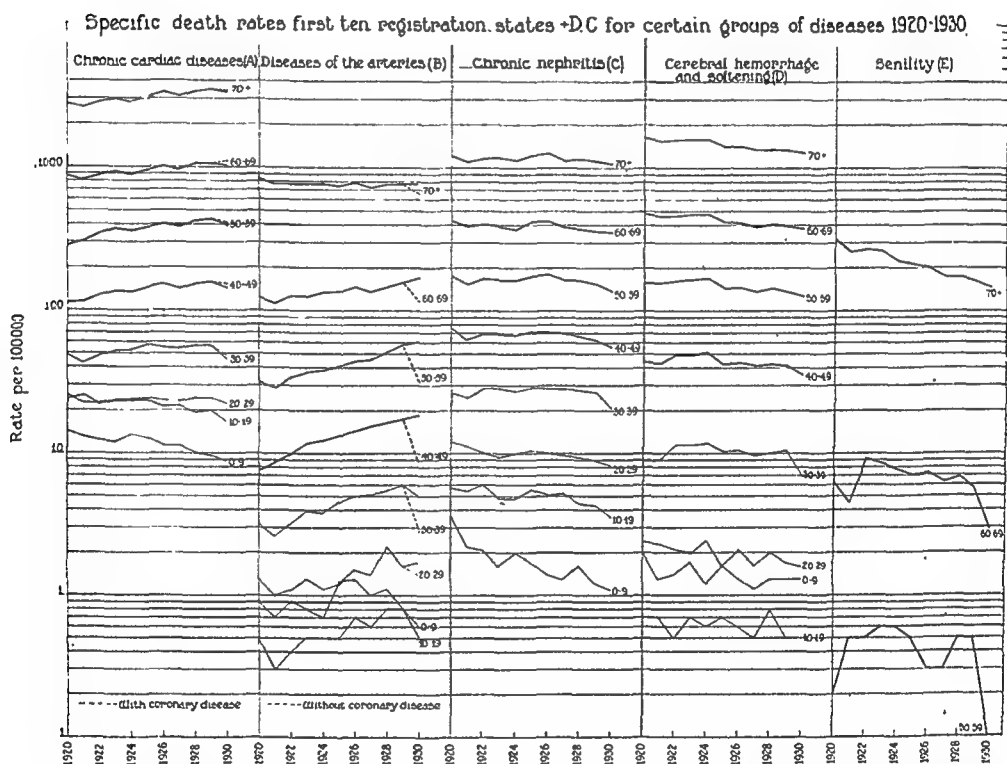


Fig. 8.—The plan of the curves describing the course of the death rates resembles Figs. 3, 4 and 5. It deals with the same rubrics A, B, C, D, E, but analyzes the data in a single decade only, from 1920 to 1930. The influence of the rates of the diseases of the coronary arteries is exhibited.

2.—In point of fact the decrease in infectious diseases is of such importance in the sixth decade that the combined rate has continued to fall, but is in the seventh decade almost unchanged (Fig. 6). Only in the eighth and ninth decades has the rate of circulatory diseases risen enough to elevate the combined rate.

3.—The fall in the total death rate observable in all decades is due to the fall in the rates in the infectious diseases. It is of great importance to point out that the saving from infectious dis-

eases is due *not* to saving in the early decades (though this is possible) for no evidence that this is so is available, but due to saving in these later decades themselves.*

- D.* A consequence of this analysis is that belief in the theory that "stress and strain" of life accounts for increase in the death rate of the cardiac diseases is unnecessary. The current state of affairs is due not to malign but to beneficent influences.
- E.* A detailed study of the rates from 1920 to 1930 (Fig. 8) shows that in A (chronic cardiac diseases) the rate rose beginning with the fifth decade. Excluding diseases of the coronary arteries the rate in B (diseases of the arteries) scarcely changed except in the third and fifth decades. In C (chronic nephritis), D (cerebral hemorrhage and softening of the brain), and E (senility) the rates fell.

CONCLUSIONS

1. The death rate from circulatory diseases has risen. It has not been great, though "great" is a relative term, and recently the increase has become ever slighter.

2. Misinterpretation of the course of events has resulted largely from changes in the entries in those diagnostic rubrics which have been predominantly employed.

3. The rise in the rate in the circulatory diseases, relatively small though it is, depends largely on the fall in the rate in infectious diseases—not that, as has often been supposed, in early life but the fall in those very decades in which a rise in the circulatory group has taken place.

REFERENCES

1. Cohn, A. E.: Heart Disease From the Point of View of the Public Health, *AM. HEART J.* 2: 275 and 386, 1927.
2. The Probability of Dying From Heart Disease. Statistical Bulletin. Metropolitan Life Insurance Co. 14: 5, 1933.
3. Bolduan, C. F., and Bolduan, N. W.: Is the "Appalling Increase" in Heart Disease Real? *J. Preventive Med.* 6: 321, 1932.
4. Albert, Henry: Increasing Mortality From Heart Disease: Suggestions as to Probable Reasons, *J. A. M. A.* 89: 1312, 1927.
5. Levy, R. L.: Discussion on Arterial Thrombosis, *Tr. A. Am. Physicians* 47: 77, 1932.

*That the slope in the curves T continues to fall in every decade suggests either that the movements in the various causes of mortality have not come to an end or that the vital statistics themselves are incompletely descriptive of the facts.

UNUSUAL SINUS TACHYCARDIA WITH OBSERVATIONS ON VAGAL ACTIVITY

DIRECT ELECTRICAL STIMULATION OF THE VAGUS NERVES IN MAN*

HENRY FIELD, JR., M.D., PAUL S. BARKER, M.D., AND
JOHN ALEXANDER, M.D.
ANN ARBOR, MICH.

THE case herein reported presents a number of unusual and interesting features. There was a remarkably rapid sinus tachycardia—200 per minute and more. There was advanced cardiac failure which was apparently due to the rapid heart rate alone. A mistaken original diagnosis led to the procedure of surgical exposure and direct electrical stimulation of the vagus nerves whereby there was demonstrated a failure of vagus control of the heart. We know of no reported case comparable in any of these respects.

CASE REPORT

The patient was a male clerk, forty years of age, weighing 55 kilograms, who was admitted to the hospital April 4, 1931. He had enjoyed good health until three weeks prior to admission when he first noticed palpitation, dyspnea, and weakness. The symptoms began suddenly and became increasingly severe so that in five days he discontinued his work and two days later went to bed.

Physical examination revealed the findings of severe congestive heart failure. There was orthopnea, cyanosis, distention of the neck veins, a large right hydrothorax and a large tender liver. There was no demonstrable peripheral edema. The heart was apparently enlarged and displaced to the left. The heart rate was about 200 per minute; the rhythm was regular; the sounds were loud and ringing; no murmurs were heard. The blood pressure was 110/95.

The Kahn reaction was negative. Repeated urinalyses were negative. The hemoglobin was 95 per cent (Sahli) and red blood cells were 5,400,000 per cu. mm., with slight variations in subsequent determinations. The white blood cells ranged from 8,200 to 10,700 per cu. mm., except for a leucocytosis of 17,400 on the eighteenth day in the hospital which followed an attack of severe, cramp-like abdominal pain of unknown origin and which promptly subsided. The basal metabolic rate, determined later when it became practicable, was minus 1 per cent.

Teleroentgenographic measurements of the heart size on admission, during convalescence and after two years of observation are tabulated in Table I. The calculations are based on the prediction tables of P. C. Hodges and Eyster¹ and of F. J. Hodges and Eyster.²

An electrocardiogram showed a tachycardia with a rate of 203 per minute. Ventricular complexes were of normal outline. The auricular complexes were partially fused with the T-waves. The cardiac rate and rhythm were not influenced by pressure upon the carotids or the eyes, and a diagnosis of paroxysmal tachycardia of supraventricular origin was made.

*From the Departments of Internal Medicine and Surgery, University of Michigan.
Read before the American Society for Clinical Investigation, May 2, 1932.

An energetic attempt was made to interrupt the supposed paroxysmal tachycardia. Although the patient had received an unknown amount of digitalis before admission, he was given over a period of five days 2.8 grams of this drug—70 per cent more than the calculated digitalizing dose.

TABLE I
TELEROENTGENOGRAPHIC DETERMINATIONS OF HEART SIZE

DATE	HEART AREA SQ. CM.			TRANSVERSE DIAMETER MM.		
	PREDICTED	MEASURED	VARIATION	PREDICTED	MEASURED	VARIATION
4/ 4/31		179	+60.9		175.	+39.6
6/ 7/31	111.2	135	+21.4	125.4	148.	+18.0
4/19/33		132	+18.9		143.	+14.4

He was also given each day either quinine hydrochloride intravenously (two doses of 0.5 gram and 0.65 gram) or quinidine sulphate orally in increasingly

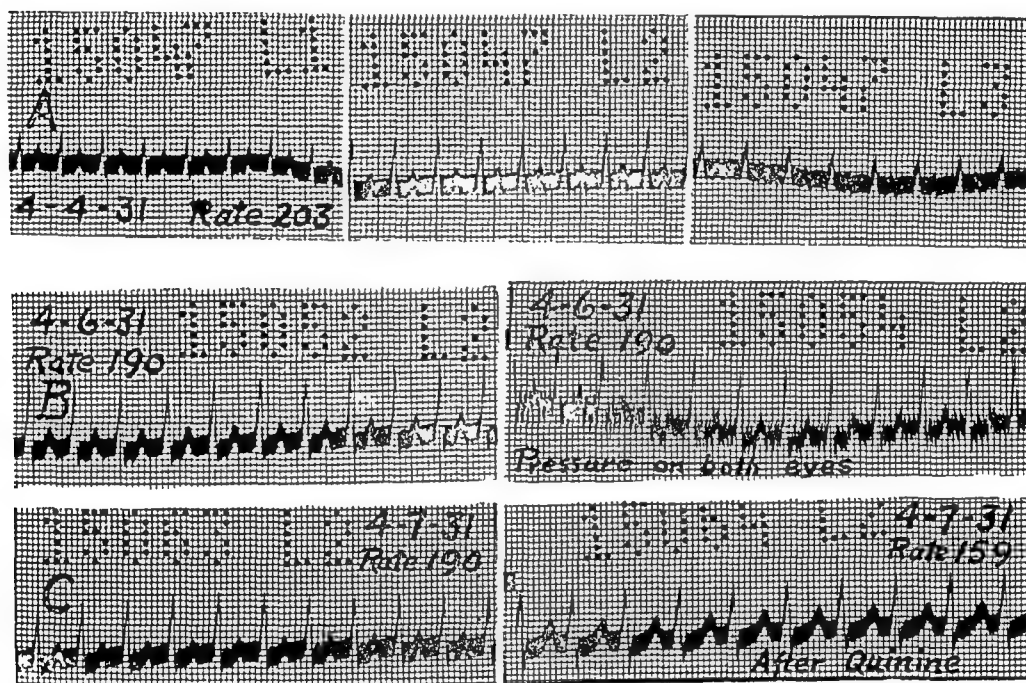


Fig. 1. A.—April 4, 1931. The three standard leads taken on admission. Extreme sinus tachycardia. These curves were originally interpreted as indicating paroxysmal auricular tachycardia. B. April 6, 1931. Lead II before and during pressure upon both eyes. No change in rate. C. April 7, 1931. Lead II before and immediately following the intravenous injection of 0.65 gram of quinine hydrochloride. The rate fell from 190 to 159 per minute.

large and frequent doses. The maximum dosage of quinidine sulphate was 3.2 grams in four doses at hourly intervals. Following the intravenous doses of quinine hydrochloride there was a slowing of the heart rate from 190 to 157 and 159 per minute, respectively, which lasted less than an hour. (Fig. 1.) Following the large oral doses of quinidine sulphate there was a comparable reduction in heart rate to as low as 144 per minute which lasted for several hours. At various times nausea, vomiting, vertigo, and mental confusion occurred. On April 9, 0.4 mg. of apomorphine was given without effect other than vomiting.

None of these measures having produced a lasting effect on the heart rate, the condition of the patient became progressively worse. The right chest was aspirated three times (on April 4, 5, and 8) and a total of 2500 c.c. of fluid was removed. Dyspnea was severe. An abundant, blood-stained, foamy sputum developed. The

patient appeared to be moribund. In what seemed to be a last desperate hope of restoring normal rhythm, direct stimulation of the vagus nerves was determined upon.

On April 10, 1931, under novocaine anesthesia locally, the left vagus nerve was exposed and isolated 2 cm. below the bifurcation of the common carotid artery. It was insulated from the patient's body by rubber dam tissue and then stimu-

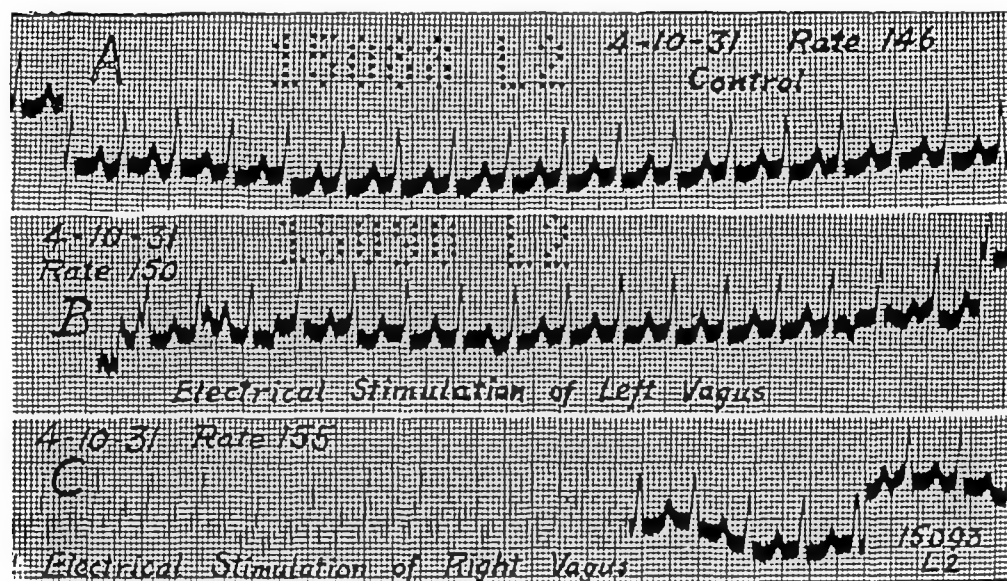


Fig. 2.—April 10, 1931. Lead II. A. Control. Rate 146. B. During and immediately following electrical stimulation of the left vagus nerve. Rate 150. C. During and immediately following electrical stimulation of the right vagus nerve. Rate 155. The oscillations caused by the faradic stimulation are plainly visible. In B the oscillations were of such large amplitude and the movements of the string so rapid that they cannot be seen in the record. The beginning of the curve marks the cessation of stimulation.

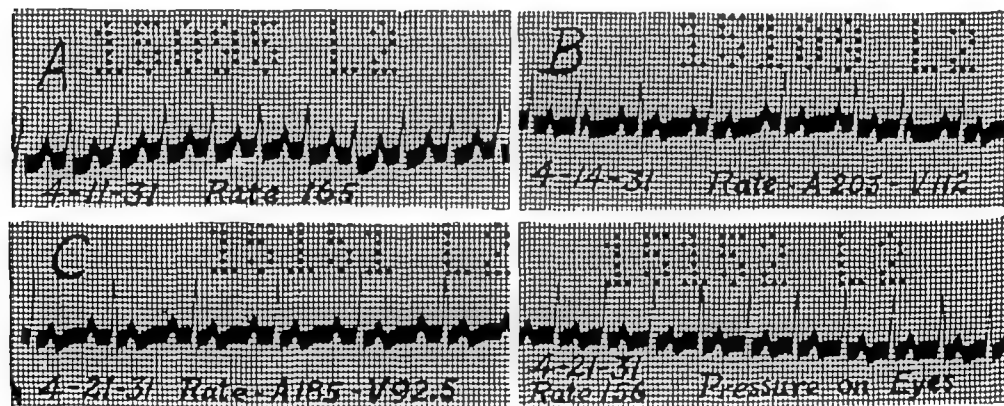


Fig. 3.—Lead II. A, April 11, 1931. Curve taken on the day following electrical stimulation of the vagi. B, April 14, 1931. Partial A-V heart-block. C, April 21, 1931. Pressure upon the eyes slowed the auricles but abolished the A-V block.

lated electrically by faradic current. The current was obtained from an ordinary dry cell and induction coil. At first the nerve was stimulated with a very weak current insufficient to cause contraction of the ribbon muscles of the neck when applied directly to them. When this was without demonstrable effect upon the heart rate, the strength of the current was gradually increased. Finally, the nerve was stimulated directly with a current of sufficient strength to cause strong, sustained

contraction of the neck muscles when applied to them. There was, however, no effect upon the heart recognizable by examining the patient or demonstrated in the electrocardiogram which was taken during the entire procedure (Fig. 2). The weaker stimulation caused pain in the neck and throat and spasmodic coughing; the stronger current caused spasmodic arrest of respiration. There were no other demonstrable changes in the patient. The right vagus nerve was then similarly exposed, isolated, and stimulated, with exactly the same results, positive and negative, as had been obtained with the left (Fig. 2). At the completion of the operation the patient's condition appeared in no way worse than at the beginning.

Following the operation the administration of digitalis in amounts approaching the limit of tolerance was continued. The usual daily dose was 0.4 gram and the average daily dose for five months was 0.38 gram. For two weeks 0.4 gram of quinidine sulphate was given by mouth every eight hours.

No effect was apparent at first except that the heart became somewhat slower (Fig. 3, A). The condition of the patient remained very precarious. On the fourth day after the operation (April 14) partial A-V block appeared and soon became a nearly constant 2:1 block (Fig. 3, B). With a slower ventricular rate the patient began to improve and by the end of another week the signs of cardiac failure had

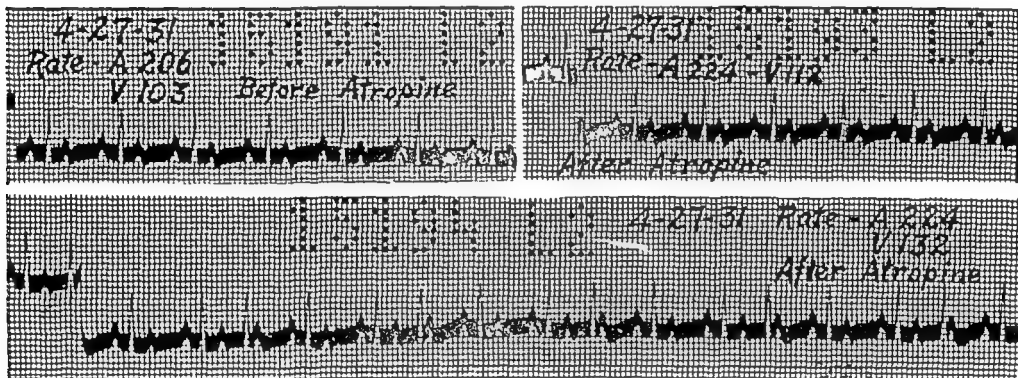


Fig. 4.—Lead II. April 27, 1931. Atropine increased the auricular rate and reduced the A-V block.

cleared. The 2:1 block remained nearly constant for three weeks, during the latter part of which there was a gradual slowing of the auricles. For another week there was a further slowing of the auricular rate with only partial A-V block. Then on May 11, one month after the operation, there was 1:1 response with a rate of 121 per minute. Further reductions in the heart rate and the development of a marked sinus arrhythmia are shown in the electrocardiograms in Fig. 5.

Other interesting electrocardiographic observations on the vagus activity were made during this period of recovery. On April 21, following strong pressure on both eyes the auricular rate slowed from 185 to 156 per minute, the A-V block was abolished, and the ventricular rate increased from 92.5 to 156 per minute (Fig. 3, C). On April 27, atropine sulphate (two doses of 0.5 mg. each, subcutaneously, one half hour apart) increased the auricular rate from 206 to 224 per minute and also reduced the degree of A-V block so that the ventricular rate increased from 103 to 132 per minute (Fig. 4).

The patient has been under observation now for over two years. Rather large doses of digitalis were required at first, to keep the heart rate below 100 per minute (0.4 gram daily for three months after his discharge from the hospital on June, then 0.2 gram daily for five months). Digitalis has been discontinued twice for periods of five and four months, respectively, during which times the pulse rate remained approximately normal. Each time a recurrence of tachycardia which

was markedly exaggerated by mild exercise (up to 200 per minute) has been controlled by 0.15 gram of digitalis daily. Repeated examinations have failed to reveal any evidence of heart disease except the slight residual enlargement noted in Table I.

COMMENT

Because of the gradual slowing of the auricular rate during the second month of observation and the constancy in the form of the P-wave throughout, we believe that we were dealing with sinus tachycardia from the first and that the patient did not have paroxysmal auricular tachycardia. The rate of over 200 is unusual and is ascribed to transient and complete vagal paralysis. The severe congestive heart

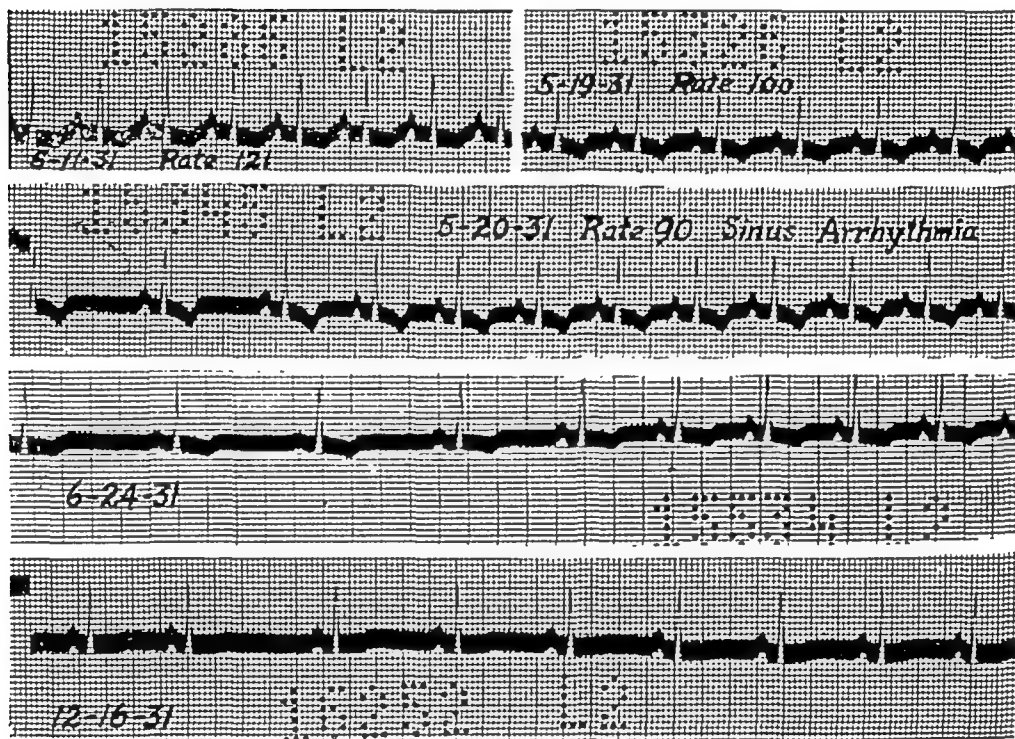


Fig. 5.—Lead II. Curves taken between May 11 and December 16, 1931. The auricles slowed gradually and the block disappeared. The sinus arrhythmia is evidence of more than ordinary vagus action upon the heart. Attention is directed to the uniformity in the contour of P. in all figures, indicating that the tachycardia was in reality an extreme sinus tachycardia.

failure which was observed seems to have been due to the rapid heart rate. It was relieved when a slower ventricular rate due to 2:1 block was established. There was no evidence at the time of admission, or in subsequent observations, of any other cause of heart failure, and the patient after more than two years has no symptoms while taking 0.15 gram of powdered digitalis leaves daily.

Failure of vagus action upon the heart was demonstrated, not only by the absence of the usual vagus reflexes, but also by the lack of effect upon the heart of strong faradic stimulation of the exposed vagus nerves. Subsequent observations demonstrated the gradual return of vagus activity.

The observations of April 21, 1931 (Fig. 3), when ocular pressure slowed the auricular rate and at the same time abolished the 2:1 block and increased the ventricular rate, are of interest. There was then a vagus influence on heart rate but no evident influence on A-V conduction. If there was any vagus inhibition of conduction, it was so slight that the slower beating auricles could break through the 2:1 block in spite of it. It would seem that the block had been maintained largely by the direct action of digitalis and quinidine upon the junctional tissues.

On April 27, 1931 (Fig. 4), a return of vagus influence on conduction was demonstrated. On this date the administration of atropine, not only increased the auricular rate, but also reduced the degree of block.

The curves taken between May 11, 1931, and December 16, 1931 (Fig. 5), show a gradual slowing of the auricular rate which is presumed to be due to returning vagus activity. The sinus arrhythmia of May 20, 1931 (Fig. 5), is an indication of quite pronounced vagus tone. The shifting pacemaker observed on June 24, 1931 (Fig. 5), may also be attributed to vagus activity.

SUMMARY

An extreme tachycardia, thought at first to be paroxysmal auricular tachycardia, persisted for four weeks and led to advanced congestive cardiac failure in an otherwise healthy man forty years of age. After the usual methods of interrupting an attack of paroxysmal tachycardia had failed, an attempt was made to terminate the rapid heart action by exposing the vagus nerves in the neck and stimulating them electrically. There was, however, no demonstrable effect upon the heart. Subsequently, partial heart-block, due to digitalis, resulted in slowing of the ventricles and was followed by improvement. Eventually, the auricles gradually slowed, the heart-block disappeared, the cardiac response to vagal activity returned, and the patient recovered. This course of events strongly suggests that the tachycardia was in reality an extreme sinus tachycardia due to failure of vagus inhibition.

The authors gratefully acknowledge the assistance of Dr. F. N. Wilson and Dr. A. G. Macleod in the electrocardiographic studies.

REFERENCES

1. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, *Am. J. Roentgenol.* 12: 252, 1924.
2. Hodges, F. J., and Eyster, J. A. E.: Estimation of Transverse Cardiac Diameter in Man, *Arch. Int. Med.* 37: 707, 1926.

CONGENITAL COMPLETE HEART-BLOCK*

AN ACCOUNT OF EIGHT CASES

MAURICE CAMPBELL, M.D., F.R.C.P.

AND

S. S. SUZMAN, M.R.C.P.

LONDON, ENGLAND

CONGENITAL complete heart-block is such an uncommon condition that an account of the following 8 cases and of one specimen from the Guy's Hospital Museum is of interest. In a recent review by Yater²⁰ only 30 of the published cases were accepted as congenital heart-block. He rejected 31 others for lack of sufficient evidence, either owing to the absence of graphic records or because there was a history of some infection which might possibly have been the cause of the block. Probably many of these were genuine cases, but even accepting them all, the number reported has not been very great.

We believe the condition to be more common than would appear from these figures, for we have seen 8 cases in the last six years. It is not difficult for some of them to be missed because the symptoms are generally slight, and the heart rate is faster than in other types of complete block, and the signs of morbus caeruleus are generally absent. If a slow pulse is found in a young man who is an athlete, it is generally sinus bradycardia. But if a slow pulse is found in a child, the possibility of complete heart-block must be remembered, and if it is present and persists, it is likely to be congenital, for infection plays a less important rôle in its production than is sometimes supposed.

Diphtheria is one of the commonest causes of temporary heart-block, which, as a rule, does not last more than a short time: when diphtheria produces a sufficiently severe myocarditis with heart-block, the symptoms are so serious that they are not likely to be missed in determining the cause of heart-block some years later. In a series of 100 cases all followed for more than five years by Jones and White¹³ no example of heart-block was found to persist, and in another series of 100 Alstead³ mentions only one, described fully elsewhere by himself and Chamberlain,⁹ where permanent heart-block resulted. Wilkinson²⁶ has not seen persistent heart-block in the diphtheritic cases he has studied at Birmingham, and Place's experience is the same.²¹

Alstead comments on the curious fact that though temporary complete heart-block is not uncommon in diphtheria, any prolongation of the P-R interval above 0.2 sec. is rarely found without actual A-V dissociation.

*From the Cardiographic Department of Guy's Hospital and the National Hospital for Diseases of the Heart, London.

On the other hand, in rheumatic carditis prolongation of the P-R interval is common, but A-V dissociation is rare. We have seen only two examples of complete heart-block due to rheumatism; one has been fully reported⁸ and both have made a complete recovery, the P-R interval returning to normal. But we have observed a girl with mitral stenosis, whose P-R interval has been regularly 0.3 sec. for three years and no dropped beat has been noted clinically or in frequent electrocardiograms, though she has been in the hospital twice for considerable periods and has been treated successfully with digitalis (up to dig. fol. gr. 3 daily) for a year.

Rheumatic fever and diphtheria only occasionally cause persistent complete heart-block, and other infectious diseases still more rarely. During the same period (1926-1932) we have seen few other examples of complete heart-block in patients under twenty-five: one may have been syphilitic, for, though her Wassermann reaction was negative, her father had died of general paralysis; the heart-block had not been noticed two years before when she had scarlet fever; so it is possible that the block was caused by this infection. We have no other case in which complete heart-block appeared to follow scarlet fever, and this is also the experience of Place.²¹

The congenital malformation most often found with heart-block is a patent interventricular septum, as shown by a systolic murmur loudest to the left of the sternum. Stokes-Adams attacks are not common, but their occurrence in infancy should be regarded as good evidence of heart-block being congenital if the graphic records are obtained only years later.

The main criteria that heart-block is congenital are:

1. A slow pulse rate at an early age.
2. Signs of congenital morbus cordis, which add considerable weight.
3. The absence of any history of infection; this is additional evidence, but is less important if the first two conditions are present.
4. Syncopal attacks in early childhood or infancy; these would be very suggestive, though such a history is not common.

We have used these criteria in diagnosing our 8 cases as of congenital origin. Four were male and 4 were female. In all of these 8 patients complete heart-block was confirmed by the electrocardiogram. So far as we know the block always remained complete; at times short records were obtained which might have been 2:1 block, but it seemed more likely that these were due to the auricle being about twice as fast as the ventricle, for we never obtained any evidence of a sudden change (Fig. 9, Lead II and Fig. 15, Lead III). At times in some cases the heart rate was faster because of frequent extrasystoles, sometimes even producing pulsus bigeminus (Fig. 4 Lead I).

The average age at which the slow pulse rate was first observed in our cases was 3.75 years: the youngest was seven months and the

TABLE 1
SUMMARY OF OUR EIGHT CASES

CASE NUMBER	SEX	AGE IN YEARS		AT PRESENT	HEART RATE AT REST		BLOOD PRESSURE		WASSERMANN REACTION	REMARKS
		WHEN SLOW PULSE FIRST OBSERVED	WHEN FIRST SEEN WITH EKG.		AURICLE	VENTRICLE	SYSTOLIC	DIASTOLIC		
1	F	0.6	1.5	3	142-150	50-65	--	--	--	Pulmonary stenosis
2	F	1	12	19	104-120	46-64	160	80	Neg.	
3	M	2	12	13	60-68	43-52	120	65	Neg.	Stokes-Adams attacks
4	M	2	12	16	136	42-50	120	50	--	
5	F	2	27	33	104-112	44-50	190	90	--	
6	M	4	4	6	88-108	39-48	140	65	--	Died
7	F	5	20	21	84-100	46-56	150	90	Neg.	
8	M	13	13	17	75-86	44-56	130	70	Neg.	
Average	--	3.75	12.6	15.7	107	50 45-55	143	73	--	--

oldest thirteen years, but he was the only one who passed his fifth year without attention being drawn to his heart.

The average age at which they first came under our observation and had electrocardiograms taken was 12.6 years. One was eighteen months, one was twenty-seven years, but most of them were about twelve years old.

All the patients are still in good health except one (Case 6), who died when six years old. Two patients (Cases 4 and 5) live too far away to return to the hospital but have replied fully to our enquiries, and all the others have been reexamined this year. Their ages are now thirty-three, twenty-one, nineteen, seventeen, sixteen, thirteen, and three years. Case 2 was fully examined when twelve years old and again when nineteen.

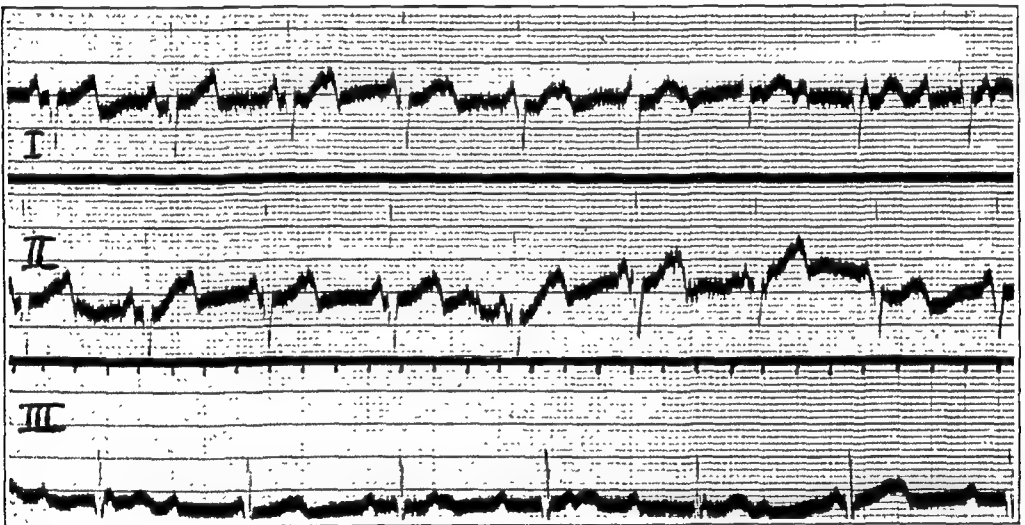


Fig. 1.—Electrocardiogram, Case 1. Complete heart-block: ventricle 75, Lead I; 65, Lead III; auricle, 142. Time marker in this and all other electrocardiograms one-fifth sec.

The first criterion of a slow pulse at an early age was therefore fairly well satisfied, though curiously enough this was never noted during the first few weeks of life. As regards the second, there were physical signs in all 8 cases to suggest congenital heart disease, generally a defect of the interventricular septum. None had morbus caeruleus and only one was diagnosed patent ductus arteriosus and pulmonary stenosis. The third criterion of the absence of infections which might have caused the heart-block was generally observed, and none gave a history of previous diphtheria or rheumatism. Case 6 had acute rheumatism, but this was two years after the heart-block had been diagnosed, and there was nothing to suggest an earlier rheumatic carditis. Stokes-Adams attacks occurred in Case 4 only. The full notes of our 8 cases follow, and certain details are summarized in Table I.

CASE NOTES

CASE 1.—Congenital complete heart-block, patent ductus arteriosus, with some degree of pulmonary stenosis. A slow heart rate and a loud systolic murmur were first noticed when patient was seven months old. When eighteen months old, she was sent to the Heart Hospital from the Infants Hospital, Vincent Square. During five weeks in the hospital her pulse rate had generally been between 50 and 60: as a rule, there had been no symptoms and she had appeared well, but in one or two attacks, perhaps brought on by coughing, her heart rate had risen to 80 and she had been rather cyanosed.

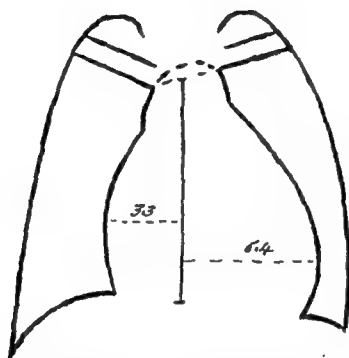


Fig. 2.—Orthodiagram, Case 1. Maximum transverse diameter 9.7 cm. (3.3 plus 6.4) in a chest of 15 cm. Scale reduced to one-quarter.

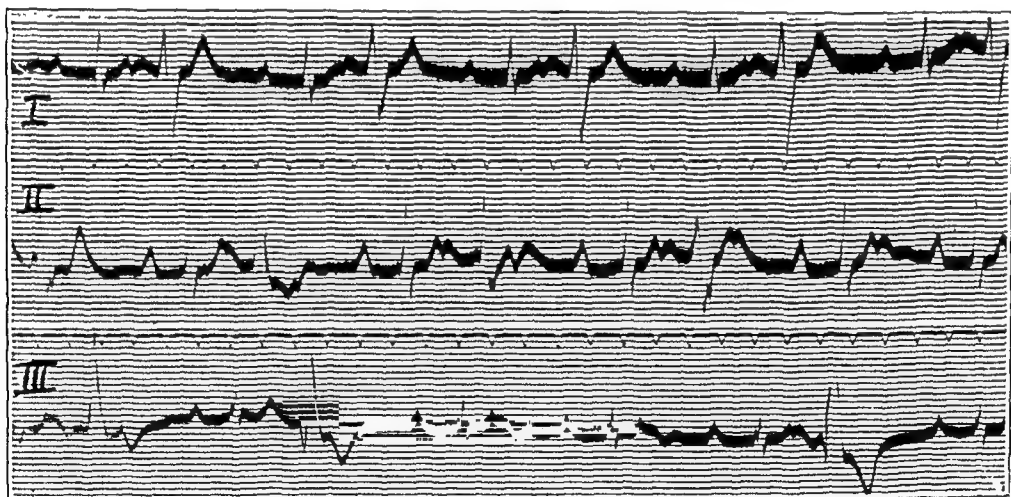


Fig. 3.—Electrocardiogram, Case 2, on 5, iii, 26. Heart-block probably complete: auricle 136; ventricle 66, or 44 with pulsus bigeminus. Another electrocardiogram of the same date showed no extrasystoles and definite complete heart-block: auricle 116, ventricle 64.

The confinement had been normal. There was no history of any infectious disease. The child appeared normal except for being rather undersized. There was no cyanosis and no clubbing of the fingers. The heart rate after resting was 52; there was complete heart-block. (Fig. 1.) The heart was enlarged to the left, with a forcible apex beat. There was a rough systolic murmur and a thrill, loudest over the pulmonary area. X-ray films confirmed the enlargement to the left and showed some increase to the right also.

When three years old, she was an intelligent child and the picture of health after sunlight treatment. There had been no more attacks of any sort, but she was

not yet able to walk. There was no cyanosis or clubbing of the fingers. The heart rate was 60 and the heart-block was complete, as it had been every time she was seen.

The heart had increased in size since her first examination, and an orthodiagram is shown in Fig. 2 (maximum transverse diameter 9.7 cm. in a chest of 15 cm.). The rough systolic murmur and thrill were most obvious further to the left in the second space, and a diastolic murmur and thrill were present, so that a diagnosis of patent ductus arteriosus could be made. In view of the enlargement of the heart,

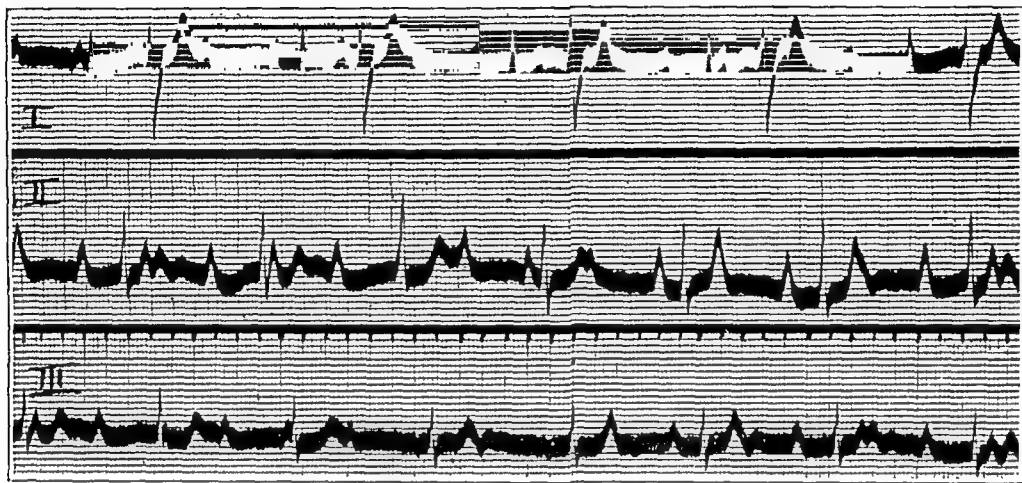


Fig. 4.—Electrocardiogram. Case 2, on 21, xii, 32. Complete heart-block; ventricle 49, Leads II and III; 33 with pulsus bigeminus on Lead I; auricle 104.

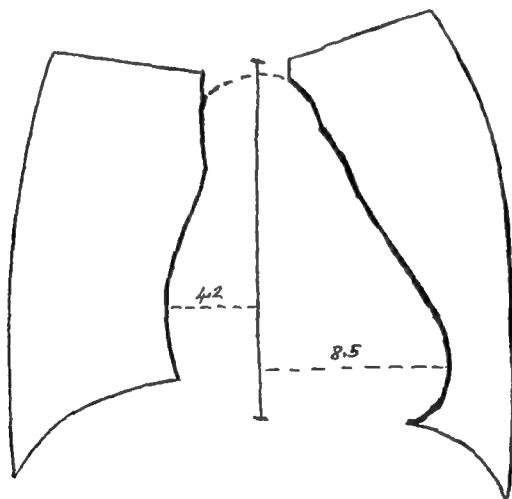


Fig. 5.—Orthodiagram, Case 2. Maximum transverse diameter 12.7 cm. (4.2 plus 8.5) in a chest of 22.8 cm. Scale reduced to one-quarter.

especially to the right, it appeared that there was also some pulmonary stenosis or a large defect of the interventricular septum.

CASE 2.—Congenital complete heart-block and patent interventricular septum. At the age of one year congenital heart disease with a slow pulse was diagnosed at a welfare clinic. When twelve years old the patient was first seen at the Heart Hospital. There was no history of rheumatism or any other infections. She looked well and the only symptom complained of was slight breathlessness on exertion, but she had never been allowed to do much in the way of exercise. The apex

beat was beyond the nipple line, diffuse and forcible. There was a systolic murmur, loudest over the pulmonary area and also heard at the apex. No thrill was felt. The heart rate was 64 to 84, this higher figure being due to frequent coupled extrasystoles and complete heart-block (Fig. 3, Lead I).

Seven years later, at the age of nineteen, she looked remarkably healthy. She was working as a shorthand typist, and had kept very well. She walked a good deal, and the only complaint was some dyspnea on running. There was no cyanosis and no clubbing of the fingers.

At first the heart was 52 with some coupling, settling down to 46 with less coupling. The electrocardiogram showed complete heart-block, often with much coupling (Fig. 4, Lead I); there was no obvious change with deep breathing. The apex beat was forcible and beyond the nipple line, and pulsation was felt above the right clavicle and over the pulmonary area. There was a fairly harsh systolic murmur loudest over the pulmonary area and conducted to the apex. The pulmonary second sound was accentuated, and an auricular third sound was often heard. No thrill was felt. X-ray films showed enlargement to the left and right, with a wide

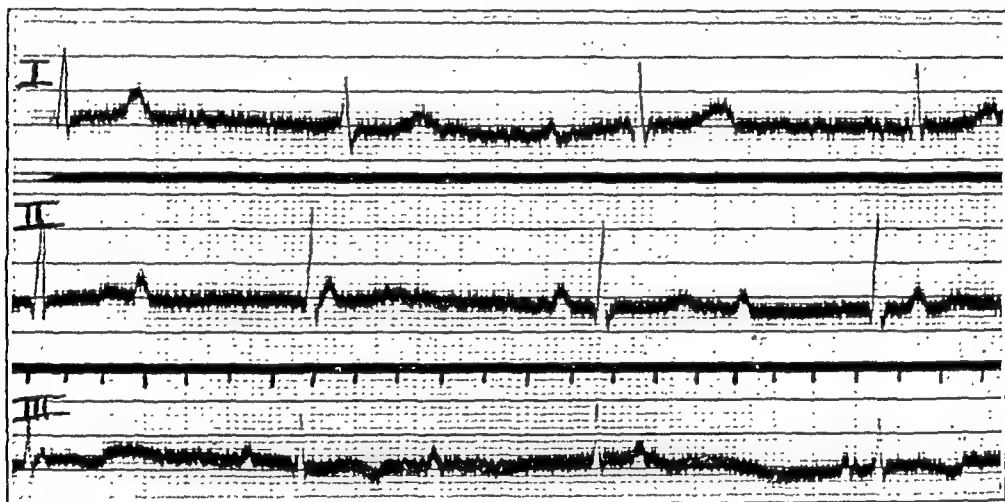


Fig. 6.—Electrocardiogram, Case 3. Complete heart-block: ventricle 43: auricle 61.

pedicle (maximum transverse diameter 12.7 cm. in a chest of 22.8 cm.) (Fig. 5). The conus and pulmonary artery and the aorta were prominent and showed vigorous pulsation. Blood pressure was 160/80. The pulse after exercise rose to 19 in the first quarter minute, dropping to 48 per minute after one minute, thus illustrating the rapid drop to normal.

Seven years after her first electrocardiogram at the hospital and eighteen years after the first observation of her slow pulse, this girl was in good health and almost without symptoms. At sight she would have been taken for a very fit, normal girl.

CASE 3.—Congenital complete heart-block with slight patent interventricular septum. This patient's heart was noticed to be slow at the age of two, when the doctor attended him for bronchitis, and again at the age of three when he had measles. These had been his only illnesses. At six years old, at a routine school examination, a heart murmur was also recorded. He was sent to the Heart Hospital when twelve years old by Dr. J. R. B. Hern; hitherto he had not been allowed to play games at school, but had led a normal life otherwise.

He was a healthy looking boy with no signs of morbus caeruleus. The heart rate varied between 44 and 48 and occasionally 52: it was regular except for an occa-

sional extrasystole. The electrocardiogram (Fig. 6) confirmed complete heart-block. The apex beat was forcible and in the nipple line. An x-ray examination confirmed slight enlargement of the heart to the left (maximum transverse diameter 10.9 cm. in a chest of 20.4 cm.), with a blunt tipped left ventricle: pulsation was well marked in the aorta and in the pulmonary artery, and this was a little fuller than usual. (Fig. 7.) There was a fairly harsh systolic murmur, heard rather widely and best over the precordium. The pulmonary second sound was accentuated and at times reduplicated. No thrill was felt. Blood pressure was 120/65. He was seen again four months later when his condition was unchanged. He had been very liberal in interpreting his permission to take more exercise and had been playing football at school with pleasure and without ill result. It was felt wiser, however, to forbid this until he had been seen for a longer time and his exercise increased more gradually. After another four months he was getting on well and still anxious to be allowed to play all games at school.

CASE 4.—Congenital complete heart-block with some patency of the interventricular septum. He was the only patient in this series with Stokes-Adams attacks. At the age of two years he was playing on the sands when he had a fit in which he went

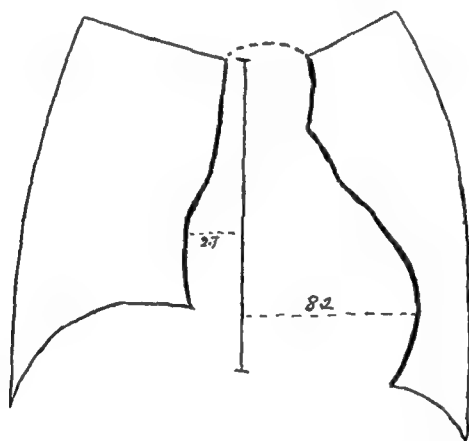


Fig. 7.—Orthodiagram, Case 3. Maximum transverse diameter 10.9 cm. (2.7 plus 8.2) in a chest of 20.4 cm. Scale reduced to one-quarter.

stiff and blue. For two years he had these attacks rather frequently, sometimes as many as three a week, but otherwise remained quite well. Unfortunately the doctor who attended him then is dead, but the patient's mother remembers his saying it was due to his heart which was always slow; i.e., in between the attacks when he appeared quite well.

During the next eight years he was much better and had only four attacks. His mother described the last one as follows: After a sudden groan he went unconscious; he was stiff and blue with no movements of any sort; she thought that he was unconscious for twenty minutes; afterward he apparently recovered very quickly. Except for these attacks he had no complaints. There was no history of rheumatism or of any infectious diseases. He was sent to Guy's Hospital by Dr. C. A. Hicks, when twelve years old.

He appeared to be a healthy boy. His heart rate at rest was generally about 42, with at times fairly frequent extrasystoles; and an electrocardiogram (Fig. 8) confirmed complete heart-block. The heart was slightly, if at all, enlarged (no x-ray examination was made). There was a systolic murmur best heard in the fourth, fifth, and sixth spaces to the left of the sternum. No thrill was recorded. Blood pressure was 120/45.

Because of the distance from London it has not been possible to get him up to the hospital again, but he has remained well, leading a normal life with no more attacks. He is now sixteen years old, and his heart rate remains slow.

CASE 5.—Congenital complete heart-block, and patent interventricular septum. Her slow pulse was first noted by her doctor when she was two years old. She attended the Heart Hospital under the care of Dr. Parkinson when twenty-seven years old; Until a year before she had always been very fit and had been able to cycle

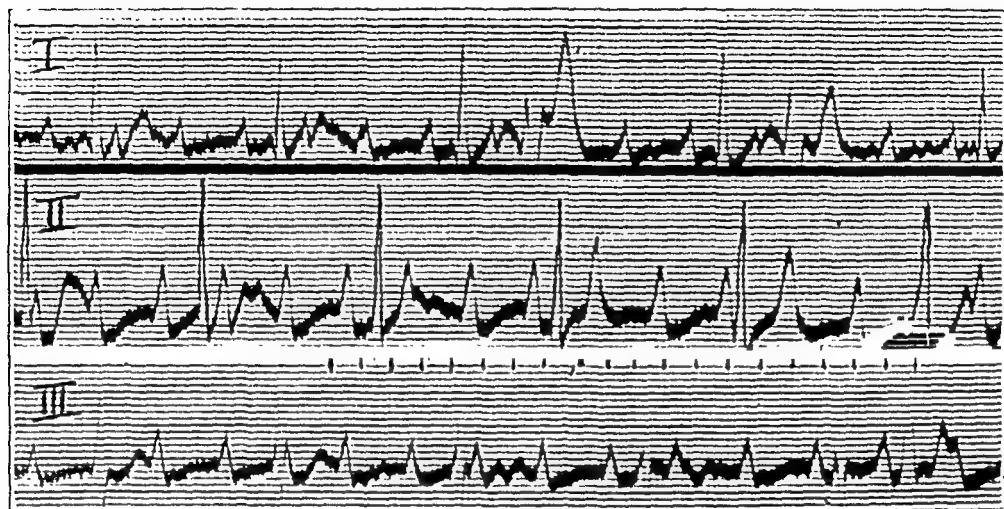


Fig. 8.—Electrocardiogram, Case 4. Complete heart-block: ventricle 50, or 35 with pulsus bigeminus; auricle 144. The P-waves were large in all the electrocardiograms taken in 1929, but he has not had one taken since.

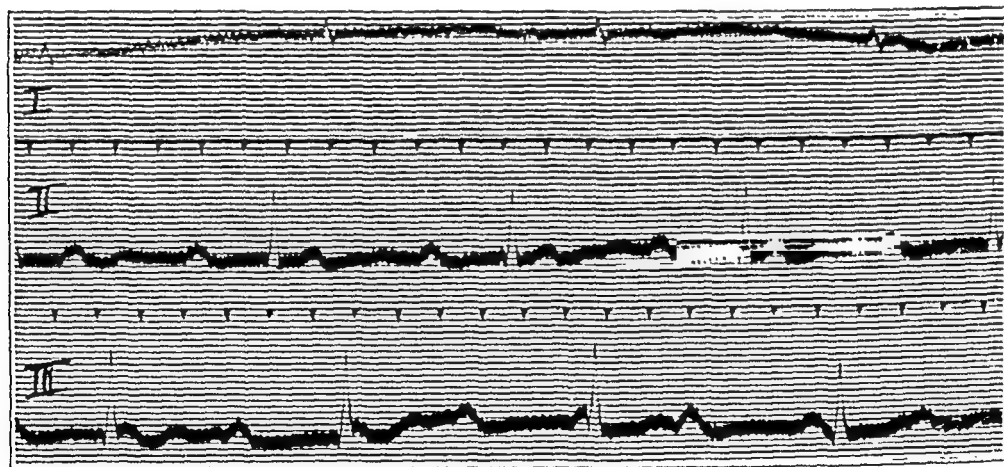


Fig. 9.—Electrocardiogram, Case 5. Complete heart-block: ventricle 52; auricle 113. Slow pulse was noticed at age of two years; patient is now thirty-three years old. In Lead II the degree of block is probably complete though the ventricular is nearly half the auricular rate.

forty miles in a day. Recently, she had been coughing and had become a little tired and short of breath, and had also lost some weight. She gave no history of rheumatic fever.

She looked well, with no signs of morbus caeruleus. Her pulse rate was between 46 and 50, and there was complete heart-block. (Fig. 9.) The heart was a little enlarged to the left, and the conus showed rather prominent pulsation. There was a systolic murmur at the apex without any thrill. Blood pressure was 190/90. No evidence of tuberculosis was found. She attended the hospital for about six months.

Now, six years later, at the age of thirty-three, she is keeping in good health, able to do ordinary housework on a farm, and to walk two miles a day. It has not been possible to examine her again, but the pulse rate is still slow.

CASE 6.—Congenital morbus cordis with complete heart-block. Death from rheumatic carditis. Patient was admitted to the Heart Hospital under Doctor Parkinson from the Fever Hospital when four years old. A slow pulse of 42 had been noticed before his attack of scarlet fever, and during the pyrexial phase it had been only 52. There was no history of rheumatism or of other illnesses.

His appearance was that of a healthy boy, and there were no outward signs of congenital heart disease, and no cardiac symptoms. There was complete heart-block and the rate varied between 32 and 48 (Fig. 10); on one occasion this faster rate was produced by atropine, but at other times it was as fast as this spontaneously. The heart was enlarged to the left; there was a forcible apex beat and a loud systolic murmur chiefly at the apex. There was no thrill. Blood pressure was 140/65.



Fig. 10.—Electrocardiogram, Case 6. Complete heart-block: ventricle 39; auricle 88.

He progressed fairly well for eighteen months, his heart rate being from 45 to 50. He was then admitted to the University College Hospital with pyrexia and painful and swollen joints, and his condition was diagnosed as congenital heart disease with subsequent rheumatic complications. Complete heart-block was again confirmed. There was no evidence of infective endocarditis. He died after two weeks, but, unfortunately, an autopsy was refused.

CASE 7.—Complete congenital heart-block with patent interventricular septum. This patient had been told that her heart was affected and that she had a slow pulse when five years old. There was no history of rheumatic fever or of any infectious diseases. She was sent to the Heart Hospital by Dr. Baron when she was twenty, complaining of feeling tired and of attacks of giddiness and faintness during the last few months. These had been occurring about once a month and sometimes she had lost consciousness. She had not been allowed to play games at school and was somewhat breathless on any special exertion. She was leading a normal life, working as a hair-dresser.

She appeared to be a healthy girl, with no signs of morbus caeruleus. Her heart rate was regular at 52, falling to 44 after she had been resting. An electro-

cardiogram confirmed the diagnosis of complete heart-block (Fig. 11). With exercise the heart quickened, being at the rate of 60 in the first quarter minute afterward.

The apex beat was forcible and just outside the nipple line. From time to time it was specially forcible and at the same time the carotid pulsation was increased. X-ray films confirmed slight enlargement to the left (maximum transverse diameter 11.7 cm. in a chest of 23.2 cm.; Fig. 12). The conus was prominent, and this and

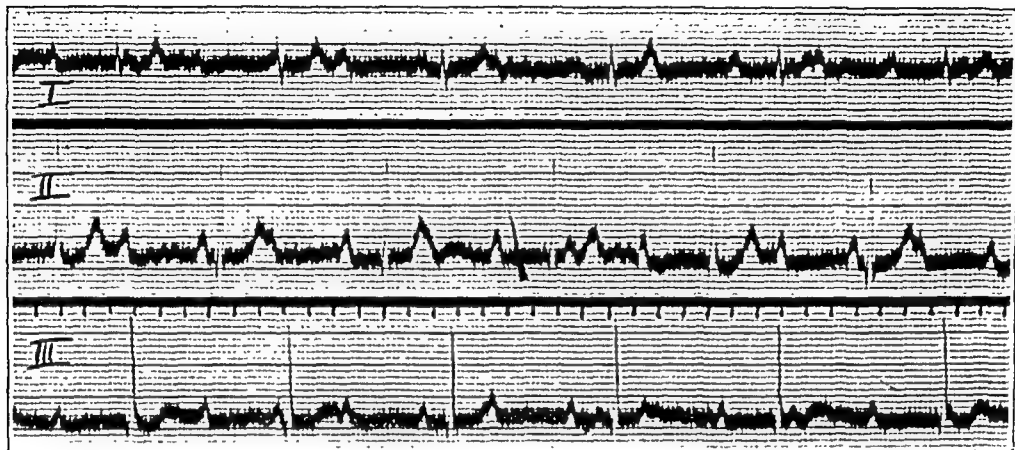


Fig. 11.—Electrocardiogram, Case 7. Complete heart-block: ventricle 46, auricle 100.

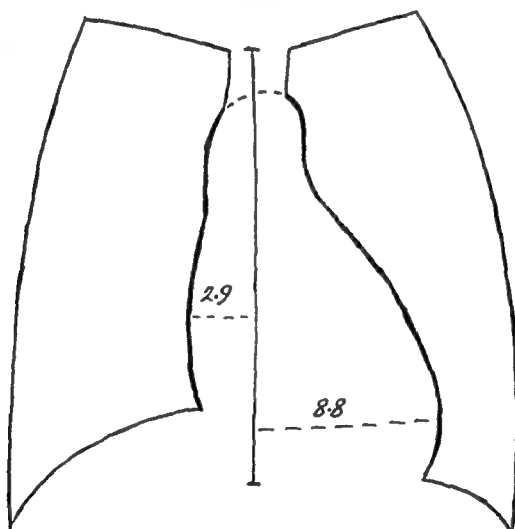


Fig. 12.—Orthodiagram, Case 7. Maximum transverse diameter 11.7 cm. (2.9 plus 8.8) in a chest 23.2 cm. Scale reduced to one-quarter.

the aortic knob and the heart itself showed very vigorous pulsation. There was a systolic murmur best heard inside the apex, and a systolic thrill in the same site. Auricular sounds were frequently heard. Blood pressure was 160/80.

The attacks of faintness and giddiness were regarded as ordinary faints and not as Stokes-Adams attacks, and this was confirmed by their disappearance with treatment—an iron tonic and reassurance—and by their occurrence under emotional stress. On two occasions when a period of faintness was observed, the pulse rate rose to 60 and was of poor volume; she was not unconscious, and as she recovered, the volume of the pulse improved and the rate fell to 44.

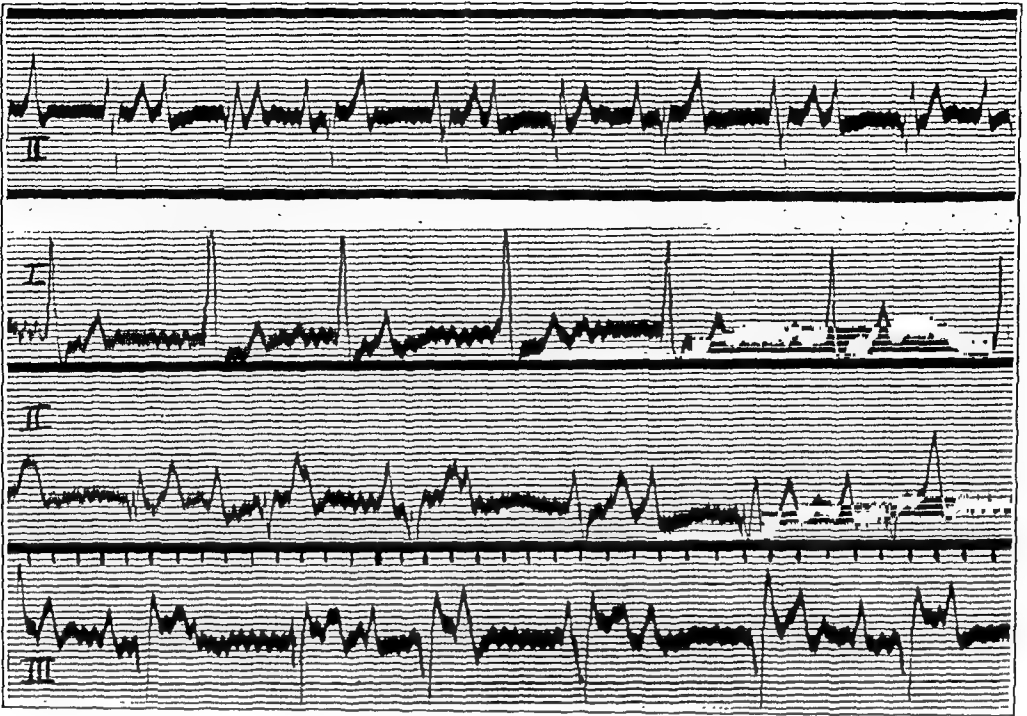


Fig. 13.—Electrocardiogram, Case 8. Complete heart-block: ventricle 51, auricle 86.



Fig. 14.—Teleradiogram, Case 8. Heart appears rather rounded and prominent to the right and in the pulmonary arc. Maximum transverse diameter 13.9 cm.

She has now been under observation for two years and has lost most of her symptoms and returned to work. Most often her heart rate on arrival in the room has been about 52, falling after she has been sitting for some minutes to 44 or 46. Sometimes it was 54 or 56, and did not always show much tendency to settle quickly to the slow rate.

CASE 8.—Congenital complete heart-block; slight patent interventricular septum. This patient was first told he had heart disease by the school doctor when he was thirteen years old, and was sent to Guy's Hospital. He gave no history of rheumatic fever or of diphtheria. He complained of no symptoms but was small for his age.

His heart rate was 54 and regular, with complete heart-block (Fig. 13). He had a systolic murmur beat heard in the pulmonary area and conducted to the apex. No thrill was felt. His heart was enlarged to the left, and the apex beat was forcible. Blood pressure was 130/70. His pulse rose to 63 after exercise.

When seen two years later, his heart rate was 52, rising to 60 after exercise. After another two years, when he was seventeen, he felt well and was working in a bottling factory. He was still small, but complained of nothing except that he was rather short of breath when playing football. The heart rate was 44 and fell to 40 after resting. The physical signs were unchanged. X-ray films confirmed the enlargement of the heart, mainly to the left (Fig. 14).

THE HEART RATE AT REST

The rate at rest generally varied between 42 and 56 and the average was 50. It may be because of this relatively fast rate that the diagnosis is not made more frequently. It was unusual to find a rate under 40, though Fig. 6 shows a rate of 38. Table II shows the slowest ventricular rate observed in our 8 and in 38 of the 45 collected cases; in the remaining 7 the block was not complete. In addition to the 30 cases collected by Yater²⁹ and our own 8, single cases have been reported by Anderson⁴ Koenen,¹⁴ Brandenburg,⁶ Godfrey and Palmer,¹² Leech,¹⁵ Nicholson,¹⁹ Sclar,²² Sprague and White,²⁴ and Wood and Rogers.²⁸ Recently Aitken¹ reported two cases of her own and added one reported by Calandre⁷ and two reported by Aylward,⁵ where an electrocardiogram has since been obtained. This with the specimen of Moxon¹⁸ makes a total of 53 cases and these are the ones referred to subsequently as collected cases.

TABLE II

SLOWEST VENTRICULAR RATE IN CONGENITAL COMPLETE HEART-BLOCK

Ventricular rate	20-29	30-39	40-44	45-49	50-54	55-59	60 and over
Number of cases	2	5	15	12	5	3	4

The rate may be much faster than this; most of our patients at times had rates of over 50 when at rest. A ventricular rate of 75 was recorded in an infant (Lead I Fig. 1); and a rate of 64 was recorded in Case 2 when the patient was twelve years old. Faster rates were noted after exercise. Although this is such a contrast to the rates found in elderly patients with degenerative changes and complete heart-block, it is not

confined to the congenital group, for sometimes rates much faster than these have been observed in complete heart-block during diphtheria.

The auricular rate was also rather fast, averaging 107; in four patients it was never noted under 100, but possibly it would have been if they had rested longer before the electrocardiograms were taken.

The Blood Pressure.—In the three elder patients this was higher than might be expected—160/80, 190/90, and 150/90 at ages nineteen, twenty-seven, and twenty-one, respectively (Cases 2, 5, and 7). In the remainder the figures were normal (Table I). There was no renal disease and no evidence of any arterial change, and probably the rise is a reaction to maintain a normal pressure during the prolonged diastolic period.

THE EFFECT OF EXERCISE ON THE HEART RATE

The ventricular rate generally returns to its normal rather quickly after exercise. It is therefore easy to miss the maximum rise, which may be quite high if the rate is taken for a short period, such as fifteen seconds. The results in four patients are shown in Table III. Except in Case 2 the fall was so rapid that the rise for a whole minute was not much, though the increase during the first fifteen seconds was considerable, all rising to 60 or over. Aitken¹ mentions rates of 57 and 58 in her two cases, and Fleming and Stevenson¹¹ also noted a rise from 49 to 68 after exercise.

TABLE III
PULSE RATE AFTER EXERCISE

	AT REST	AFTER EXERCISE					
		QUARTER MINUTE				FIRST MINUTE	
		1	2	3	4		
Case 2 (a)	46	17	15	13	12	57	
(b)	46	19	15	13	12	59*	
Case 3 (a)	48	14	13	12	12	51	
(b)	46	15	13	12	12	52*	
Case 7	48	15	14	12	11	52	
Case 8	56	16	16	16	15	63*	

*Three minute exercise; others were for shorter periods.

In Case 3 this was confirmed by taking an electrocardiogram as soon as possible, and then, though a rather longer interval elapsed while the patient was lying down and the instrument being adjusted, a ventricular rate of 56 was recorded, where it had been 46 just before. On this occasion the auricular rate could also be measured, and it was 97 instead of his usual 60 to 68; i.e., the auricular rate had increased just as much as one would expect after exercise in a normal person, and the ventricular rate had increased, though not to the same extent. It seems most likely that the chemical changes in the blood, especially the increased CO₂ content, are responsible for the increase of rate.

In ordinary cases of heart-block the rise in ventricular rate with exercise is less than this, but occasionally it is even more. In one of our patients in whom the rate at rest was generally 42 to 50, it rose to 70 after exercise.

Liljestrand and Zander¹⁶ have investigated one case very thoroughly, and their work is useful in understanding the circulation in heart-block. He was a young man of twenty who was able to take part in strenuous games, and to swim "for as long as he liked." When three years old he had pneumonia and was found to have an irregular pulse. After that, he was liable to fainting attacks, and when five years old, he was sent to the hospital where he was found to have a ventricular rate of 45 to 50 and complete heart-block. He had steadily improved from then on and had lost any tendency to fainting attacks. It is possible that the block was congenital and not due to his pneumonia. His ventricular rate increased up to over 100 with strenuous exercise.

The minute volume of his circulation was about normal, but on one occasion when the rate was 37 the output per beat was 123 c.c. (i.e., minute volume 4.5 liters) compared with a normal when the rate was 70 with an output per beat of 70 c.c. (i.e., minute volume 4.9 liters). With violent exercise the minute volume was increased to 16.4 liters (ventricular rate 94 with an output per beat of 174 c.c.): a control taking the same exercise increased his minute volume to 19.8 liters (ventricular rate 140 with an output per beat of 140 c.c.). Lundsgaard¹⁷ also found the output per beat raised to about 150 c.c. in complete heart-block. This increased output per beat is associated with the forcible beat of the ventricle to be seen when many of these patients are x-rayed. It explains why they have no undue dyspnea with moderate exertion, in spite of their slow heart rate.

THE EFFECT OF ATROPINE ON THE HEART RATE

In two of our cases observations were made after injection of atropine. In Case 3 1/150 gr. did not increase the auricular rate above 70 (thirty-five minutes) or the ventricular above 49 (forty minutes), 60 and 45 being the rates at rest that morning for the auricle and ventricle, respectively. In Case 7 1/150 gr. raised the auricular rate to 120 from 77 and the ventricular rate to 56 from 44 after forty minutes.

Aitken¹ has collected 12 cases in which the effect of atropine was observed. Auriculoventricular dissociation was never restored, and she rightly adduces this as showing that the vagus is not the cause of the block. Both auricular and ventricular rates were considerably increased, in four, but in two the auricle was faster and the ventricle was unchanged. Atropine was without effect on either, in the remaining six; so possibly the dose was insufficient. In Leech's case¹² the ventricle increased from 47 to 70 in twenty minutes, but generally the greatest effect was

noted in about thirty-five to forty minutes—94 from 62, and 83 from 55 in Aitken's two cases, and 78 from 56 in one of Fleming's cases.¹¹

THE EFFECT OF FAINTNESS ON THE HEART RATE

The main complaint for which one patient (Case 7) came to the hospital was faintness, and we were fortunate in observing this twice. We had already formed the opinion that the faints were of vagal origin

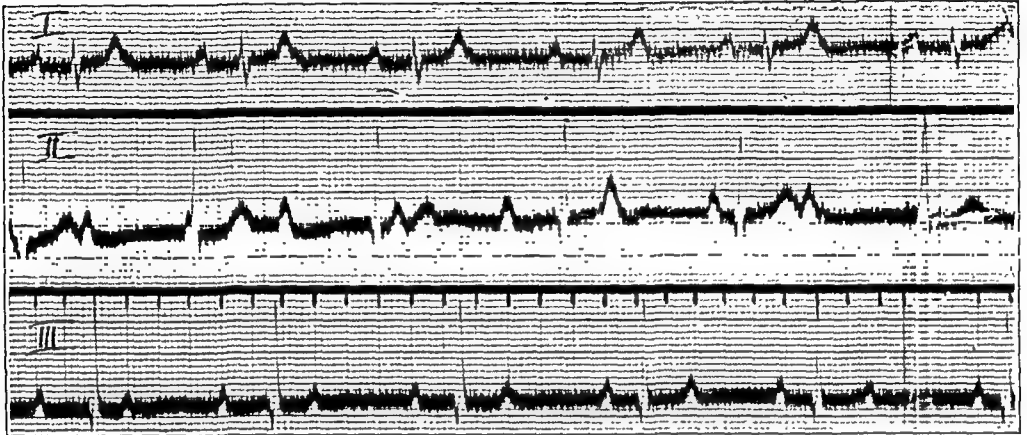


Fig. 15.—Electrocardiogram, Case 7, just after the onset of faintness, forty minutes after atropine had been given. Lead I: ventricle 53, auricle 107; Lead II: ventricle 52, auricle 92; Lead III: ventricle 50, auricle 99.

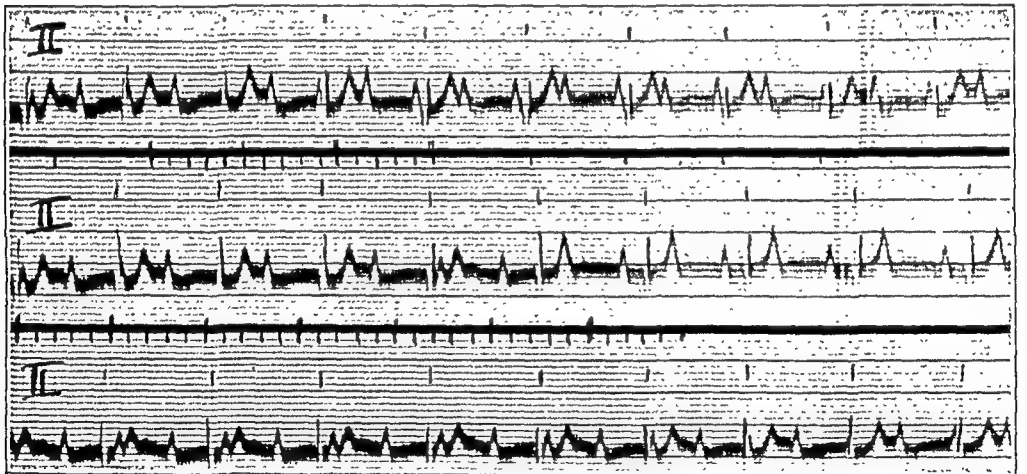


Fig. 16.—Electrocardiogram, Case 7, taken three minutes after Fig. 15, during an attack of faintness. Lead II only: ventricle 56 to 51, auricle 112 to 109.

and not Stokes-Adams attacks, from the general description, from their recent onset, and from the effect of emotion. This view was confirmed by their disappearance with treatment and by her return to work.

On one occasion atropine had been injected forty minutes before, and no doubt she was tired with repeated examinations and electrocardiograms. Just before Fig. 15 was taken, she complained of "a funny feeling in the stomach." Three minutes later while still sitting in the chair she "fainted." She was pale and there was no cyanosis. She was

not unconscious. Her pulse rate was 60, and no period of a slow pulse was noted, although she was under almost continuous observation. This is in contrast to the ordinary faint where the weak rapid pulse comes later, and where at the beginning the pulse is slow and sometimes not quite regular. Fig. 16 was taken during the attack which lasted about five minutes. In ten minutes she felt well and was able to walk home. The other observed attack was very similar.

ASSOCIATED CONGENITAL LESIONS

In most of the reported cases there has been some degree of cardiac enlargement, but generally it has been slight or moderate, as was true in our 8 cases. It is often easy to say that a patient has congenital heart disease but more difficult to decide exactly what the congenital abnormality is. None of our 8 cases had obvious cyanosis or clubbed fingers or the complete picture of morbus caeruleus. All had signs which suggested that there was a patent interventricular septum, and one patient probably had some degree of pulmonary stenosis.

This agrees with most other reports of congenital heart-block. Of our 8 and the 45 collected cases 8 (15 per cent) had obvious cyanosis at rest, generally with clubbed fingers; in these there was gross congenital heart disease, most often pulmonary stenosis with other associated lesions.

Apart from this 15 per cent, another 35 (67 per cent) had signs of a patent interventricular septum. In the remainder the signs were too slight to make a definite diagnosis, but there were only three or four in which the authors found no signs to suggest structural congenital disease of slight degree. Among this group with patent interventricular septum there were 13 (25 per cent) with some degree of cyanosis, though often it was only slight or only present on exertion. There were also the 8 with more obvious cyanosis at rest, but this still leaves more than half (60 per cent) in whom no cyanosis was observed.

CASES WITH POSTMORTEM EXAMINATION

We have found published reports of only three cases and add a fourth of a specimen, so far as we know not published previously.

I. Moxon's case (Guy's Hospital Museum. Specimen 2317.).—A boy, aged two years, with extreme cyanosis and dyspnea, was admitted under Dr. Moxon in 1879. The second sound was greatly accentuated in the pulmonary area and the pulse rate was 25 a minute. He was apparently well until he was a year old, when, after having whooping cough, he began to be cyanosed. This became much worse seven months before his admission. He died suddenly after he had been in the hospital a month.

The pulmonary artery was completely occluded at its origin and was only a small tube up to the entrance of the patent ductus arteriosus, where it became of normal size. There was a large opening in the upper

part of the interventricular septum, and the right ventricle was greatly hypertrophied, the wall being thicker than that of the left. Except for the condition of the heart the other viscera were normal.

The slow pulse and the cyanosis were not noted until after his whooping cough, but in view of the condition of the heart it is certain that the lesion was congenital and therefore it is probable that the slow pulse was also congenital, the illness having made his condition much more noticeable. Only one other case has been recorded with such a slow pulse rate (D'Espine and Cottin¹⁰), but it is difficult to think of any diagnosis but complete heart-block. The earliest generally accepted case is that of van den Heuval in 1908.²⁵

II. Wilson and Grant's Case.²⁷—A child of fourteen months with incomplete heart-block. Examination showed complete stenosis of the pulmonary artery with a large patent ductus arteriosus and a common ventricle with only the rudiment of an interventricular septum in the form of a rounded muscular prominence on the posterior wall. Histologically, the auriculoventricular node was well developed, and situated in the interauricular septum and the central fibrous body. But the fibers coming from it were interrupted and broken up by the fibrous tissue of the central fibrous body. The fibers ultimately reunited, however, and divided normally into right and left branches.

III. Perotti's case.²⁰—A child three days old, in whom examination showed complete absence of the membranous portion of the interventricular septum. Histologic examination was not made.

IV. Yater's case.²⁹—A child a few days old, in whom examination showed transposition of all the viscera and great vessels, except the ventricles of the heart. The ductus arteriosus was patent, and there was a patent foramen ovale and a small patency in the interventricular septum. The sino-auricular node was found in the wall of the auricle on the left side (structurally this corresponded with the right auricle). The auriculoventricular node lay against the right side of the central fibrous body in the auricle of the right side. The node was separated into two parts by fibrous tissue from the central fibrous body, thus separating the A-V node from the bundle of His.

PROGNOSIS

As few of the patients described have been over twenty years of age and as none seems to have been older than our patient (Case 5), it might seem that the outlook is good for a time but that few survive long in adult life. Probably this is incorrect and when patients have been followed for a longer time they may be found in good health at a more advanced age. They may not have been reported at older ages because the possibility of the block being congenital has not been considered.

In some cases, especially in patients who have died in the first few weeks of life, the associated malformation of the heart and not the heart-block was the cause of death. Stokes-Adams attacks increase the risk of sudden death, but they are found in a small minority only and the risk is less than might be expected.

Nine of the 53 patients are known to be dead. Four died in early infancy, probably because of the associated congenital malformations. Our patient (Case 6) died of infective endocarditis, an added complication of his congenital heart, and the block was probably without significance. The remaining four died suddenly. The first, whose sister also has congenital heart-block, had a patent interventricular septum and occasional attacks of cyanosis; at three months old the pulse became irregular and she died in one of these attacks.⁵ The second died suddenly at two years, having had gross cyanosis and dyspnea for some time.¹⁵ The third had extreme cyanosis and pulmonary stenosis and died suddenly at the age of nine years.²³ All these three had serious congenital heart disease as well as block and are mentioned here only because of the suddenness of their deaths. Were it not for the next case, one might feel that the prognosis was excellent as regards the heart-block and need be considered only as regards the associated malformation. The fourth had no other signs of heart disease and no symptoms, and was accustomed to bathing and strenuous exercise, but she died suddenly when thirteen years old just as she was going into the water.² In her, at any rate, a fatal Stokes-Adams attack seems the likely explanation, but curiously enough none of these four gave a history of syncope attacks, though these were present in 8 other patients, all, so far as we know, still alive.

CONCLUSIONS

Congenital heart-block is probably more common than has been thought, and this possibility should be remembered when treating children with a slow pulse. The block is more often complete than partial.

The ventricular rate is usually between 42 and 56 and quickens to 60 or faster with exercise. Stokes-Adams attacks are not common but occur in about one-eighth of the patients, generally in the first few years of life.

As a rule, there is some degree of patency of the interventricular septum, and the heart is a little enlarged, often to both sides, with marked pulsation and some prominence of the pulmonary are. More serious abnormalities and typical *morbus caeruleus* are less common.

Provided that the associated malformation is not in itself serious, the outlook is good. Sudden death is a rare catastrophe. Usually, the subject is able to lead an active life with little or no dyspnea, and survives to adult life or much longer.

REFERENCES

1. Aitken, J. K.: *Lancet* 2: 1375, 1932.
2. Aldrich, C. A.: *Tr. Chicago Pediat. Soc.* June 6, 1927.
3. Alstead, S.: *Quart. J. Med. (New Series)* 1: 277, 1932.
4. Anderson, G. H.: *Northwest Med.* 28: 227, 1929.
5. Aylward, R. D.: *Brit. M. J.* 1: 943, 1928.
6. Brandenburg, K.: *Med. Klin.* 38: 1464, 1929.
7. Calandre, L.: *Arch. cardiol. y hemat.* 2: 225, 1921.
8. Campbell, M.: *Lancet* 2: 180, 1931.
9. Chamberlain, E. N., and Alstead, S.: *Lancet* 1: 970, 1931.
10. D'Espine, A., and Cottin, E.: *Rev. méd. de la Suisse Rom.* 35: 516, 1915.
11. Fleming, G. B., and Stevenson, M. M.: *Arch. Dis. Child.* 3: 221, 1928.
12. Godfrey, V. W., and Palmer, R. S.: *New England J. Med.* 207: 575, 1932.
13. Jones, T. D., and White, P. D.: *AM. HEART J.* 3: 190, 1927.
14. Koenen, H. P. J.: *Nederl. tijdschr. v. geneesk.* 49: 600, 1930.
15. Leech, C. B.: *Am. J. Dis. Child.* 39: 131, 1930.
16. Liljestrand, A., and Zander, E.: *Acta med. Scandinav.* 66: 501, 1927.
17. Lundsgaard, V.: *Deutsch. Arch. f. klin. Med.* 120: 481, 1916.
18. Moxon, W.: *Guy's Hosp. Museum Cat., Specimen 2317, Autopsy 403, 1879.*
19. Nicholson, G., Shulman, H. I., and Green, D. L.: *Am. J. Dis. Child.* 36: 580, 1929.
20. Perotti, D.: *Boll. d. Soc. med-chir. di Pavia.* 3: 1, 1928. (Quoted by Yater.)
21. Place, E. H.: *New England J. Med.* 207: 525, 1932.
22. Sclar, M.: *AM. HEART J.* 6: 289, 1930.
23. Shapiro, M. J.: *Minnesota Med.* 10: 566, 1927.
24. Sprague, H. B., and White, P. D.: *M. Clin. N. Amer.* 10: 1235, 1927.
25. Van den Heuvel, G. C. J.: *Proefschr. aan de Ryhs Univ.* 12: 142, 1908. (Quoted by Yater.)
26. Wilkinson, K. D.: *Personal communication, 1933.*
27. Wilson, V. A., and Grant, R. T.: *Heart* 12: 295, 1925-1926.
28. Wood, W. A., and Rogers, H.: *California and West. Med.* 36: 397, 1932.
29. Yater, W. M.: *Am. J. Dis. Child.* 38: 112 and 551, 1929.

RUPTURE OF THE RIGHT AURICLE OF THE HEART*

CASE REPORT WITH ELECTROCARDIOGRAPHIC AND POST-MORTEM FINDINGS

G. M. CLOWE, M.D., E. KELLERT, M.D.,
SCHENECTADY, N. Y.
AND L. W. GORHAM, M.D.
ALBANY, N. Y.

INTRODUCTION

OUR knowledge of rupture of the heart dates from the time of Harvey¹ who in 1647 described the first case, since which report there have been numerous contributions to the subject, dealing for the most part with ventricular rupture. The frequency of this finding at post-mortem examination is apparently increasing. There are found wide variations in the incidence of cardiac rupture according to the statistics which are consulted. Thus the older figures cited by Krumbhaar and Crowell² are as follows: Philadelphia General Hospital, 7 cases in 16,000 autopsies; and Romeik of Munich, 7 cases in 13,000 autopsies. More recently De la Chapelle³ has reported 20 cases among 15,000 autopsies performed by the medical examiner's service in New York City, while Benson, Hunter and Manlove⁴ record 40 ruptures among nearly 7,000 autopsies. The records of 1,454 consecutive post-mortem examinations at the Albany Hospital contain 6 instances of cardiac rupture.

Krumbhaar and Crowell² in 1925, and Davenport⁵ in 1928 in a supplementary analysis, have made a most exhaustive statistical study of all the cases of cardiac rupture in the literature from 1872 to 1928. In a grand total of 710 cases they found the site of the rupture distributed as follows: left ventricle 566 (79.8 per cent), right ventricle 76 (10.7 per cent); right auricle 38 (5.3 per cent), left auricle 13 (1.8 per cent), and miscellaneous 17 (2.4 per cent).

It is well known that cardiac rupture is an accident chiefly confined to the left ventricle, and that it occurs principally in the advanced years of life—the decades from fifty to eighty years. Furthermore it is practically always secondary to cardiac infarction, the result of coronary artery occlusion, by either thrombosis or fibrotic narrowing. It is indeed doubtful whether a perfectly healthy heart is ever spontaneously ruptured, as signs of pre-existing disease can usually be found.

The facts known about rupture of the auricle are fewer and less clearly defined than those pertaining to the ventricle. Rupture of the

*From the Ellis Hospital Laboratory, Schenectady, N. Y., and the Department of Medicine, Medical Department of Union University, Albany Medical College, Albany, N. Y.

auricle is a rare but not by any means unique condition. In the series referred to above there was a total of 51 cases, or 7 per cent, and the right auricle was affected three times as frequently as the left. A review of the literature reveals that most of the communications contain but brief clinical and pathological notes. No case has thus far been reported in which serial electrocardiograms were taken immediately following the onset of symptoms.* Microscopic examination of the ruptured auricular wall has been made in only a small percentage of the cases described. The following case with serial electrocardiographic observations and histological study is therefore considered worthy of record:

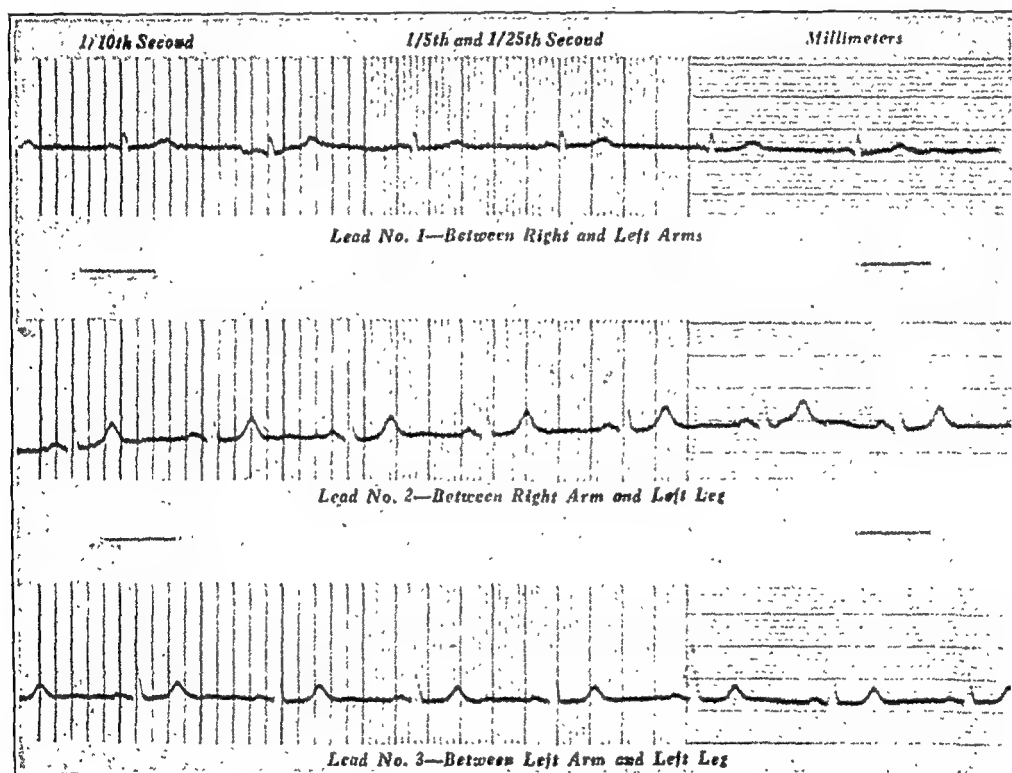


Fig. 1.—Record of April 4, 1930.

CASE REPORT

The patient, an electrical engineer, forty-three years of age, married, with two healthy children, had always enjoyed excellent health. There was no history of preceding cardiac disease or of syphilis. On the evening of April 3, 1930, while rubbing himself with a towel after a bath, he was suddenly seized with excruciating substernal pain which radiated to the neck and head. He fell to the floor unconscious but after about fifteen minutes revived, vomited, and helped himself to bed. The pain persisted during the night, in the chest, head and back of the neck. His physician, summoned the following morning, found the patient, a sparely nourished, well-developed man, looking pale and ill but not dyspneic—the pain subsiding—temperature 100° F., pulse 80, regular, good quality in the right wrist, but not

*Lisa and Ring⁶ have published two electrocardiographic tracings taken two years and one month respectively before death. Their case showed an infarct of the left ventricle, as well as rupture of the left auricle.

detectable in the left. The heart was normal in size and outline, its action regular, and a soft systolic murmur was heard over the aortic area, transmitted to the right side of the neck. There was no pericardial friction rub. Blood pressure in the right arm was 150/50 mm., in the left a few beats came through at 60 mm., but the diastolic pressure could not be determined. There were no color changes or disturbances of sensation in the two hands. Physical examination was otherwise entirely negative.

During the next three days the patient's condition did not change essentially. Slight fever continued, the pulse ranged from 80 to 100; the pain had diminished to the level of a substernal soreness; the systolic murmur disappeared; no cardiac friction developed, and the inequality of blood pressure in the two arms persisted. On April 7, following an examination in which an enfeeblement of the heart sounds

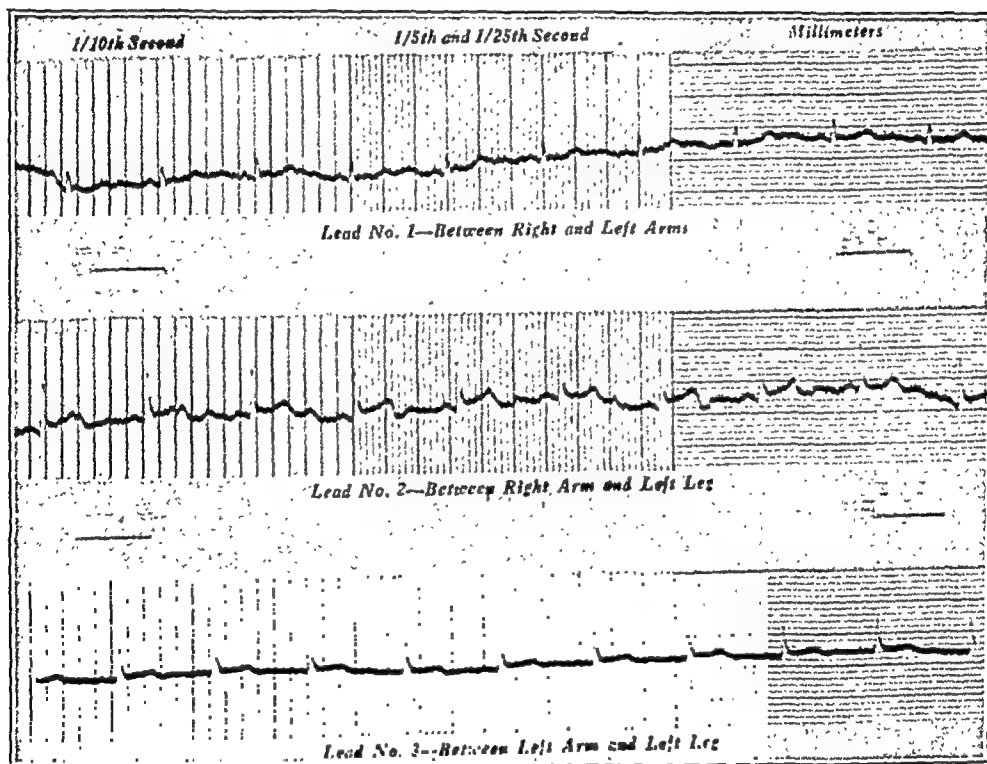


Fig. 2.—Record of April 6, 1930.

and slight dullness at the bases of the lungs with a few fine râles were noted, the patient suddenly made several convulsive movements, the face became livid, the pulse disappeared from the right wrist, and death ensued at once.

Laboratory Data.—Leucocyte count 9,800; polymorphonuclears 67 per cent, lymphocytes 30 per cent, monocytes 2 per cent, eosinophiles 1 per cent. Red cells normal. Urine examination negative. Blood Wassermann reaction negative. Electrocardiograms were taken on April 4, 6, and 7 (Figs. 1, 2, and 3).

Fig. 1. Record of April 4, 1930. Rhythm regular. Rate 65-70. A-V conduction normal. QRS width within normal. S-T time normal. P-waves practically normal; possibly a little widened. R_1 is low; R_2 is normal in height but slurred and widened to nearly 0.08 sec. R_3 is slightly lower than R_2 and also slurred and widened a little. S-waves absent. T-waves normal.

Diagnosis.—A slight delay in intraventricular conduction is indicated by Leads II and III.

Fig. 2. Record of April 6, 1930. Rhythm regular. Rate about 100. A-V conduction normal. QRS width normal in Lead I but increased in Leads II and III, owing to the elevated take-off of the S-T line. S-T time not measurable owing to the deformity of T. The P-waves show no significant change. R_1 is unchanged. R_2 is lower than on April 4, as is R_3 also. S-waves absent. A change in the S-T line has occurred. In Lead I it is convex upward and in Lead II it is reversed, concave, and takes off well above the P-R level. In Lead II S-T is horizontal but takes off a little above the P-R level. The form of T is variable in Leads I and II especially and in those leads there is an extra wave of variable shape and height after the T-wave.

Diagnosis.—The cardiogram strongly suggests a coronary occlusion. In any event, some myocardial injury has occurred.

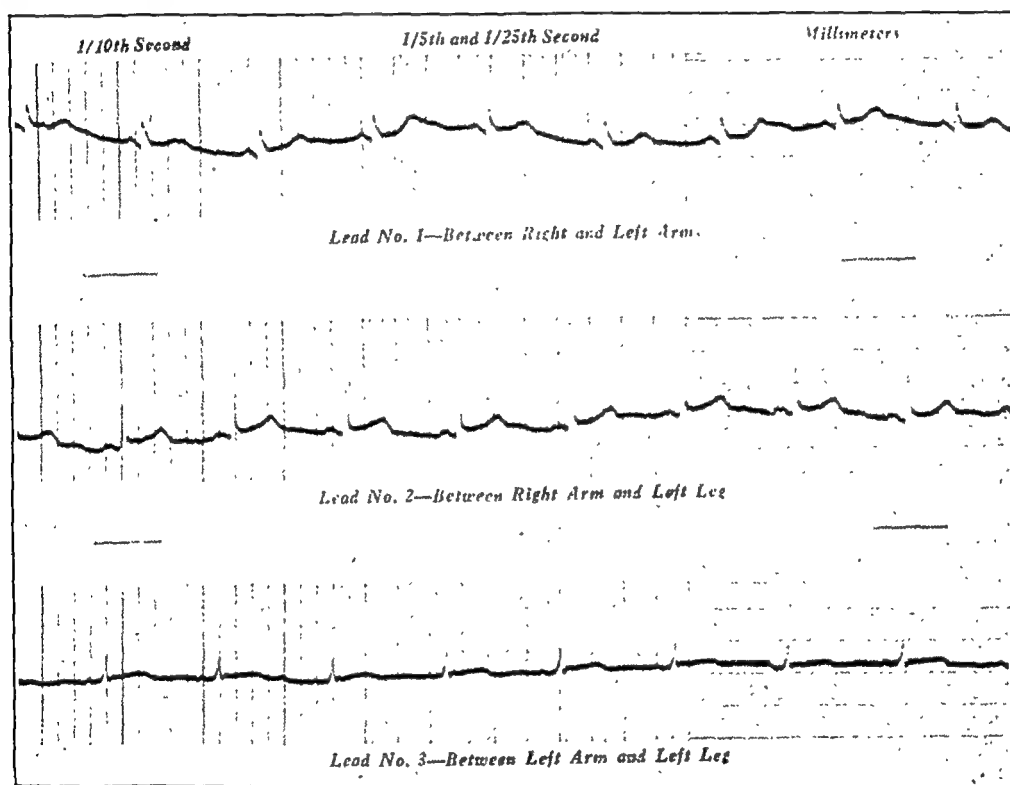


Fig. 3.—Record of April 7, 1930.

Fig. 3. Record of April 7, 1930. Rhythm regular. Rate about 85. A-V conduction normal. The QRS (actually only the R) width has increased in Lead I since April 6, and decreased somewhat in Leads II and III. S-T time not measurable. There are slight changes in the P-waves. R_1 is widened since yesterday and the S-T line is now concave and takes off above the P-R (isoelectric) level. R_2 is unchanged. The S-T line of Lead II still takes off above the P-R level. R_3 is lower than on yesterday. T_1 is higher than it has been on the two previous days and is variable in form. T_2 is less variable than on yesterday. The extra wave after it is inconspicuous today.

Diagnosis.—Unchanged (see report of April 6). In summary one may say that the various changes described in the QRST complex indicate a suddenly developing disturbance of the ventricular musculature, and they further suggest a decline in myocardial efficiency, due possibly to a coronary occlusion. (Since a calibration

curve is not given for the record of April 6, too much importance should not be given the comparisons of wave amplitude.)

Portable x-ray film of chest taken April 7, 1930, the day before death, showed diminished transmission of rays through the lower right chest. The heart is apparently enlarged, and the shadow of the great vessels measures 9.3 cm. This change cannot be considered as of diagnostic value, because the plate was taken with the patient lying in bed, and not at six feet; hence a certain amount of distortion must have occurred. A slight prominence of the shadow in the region of the right auricle is noted.



Fig. 4.—Photograph of heart. Reconstruction after dissection. Note line of rupture in right auricle.

Diagnosis.—A positive clinical diagnosis was not made. In favor of coronary occlusion were the history of long-continued severe substernal pain, with fever, and suggestive electrocardiographic changes. The differences in blood pressure on the two sides and the probable increase in the mediastinal shadow suggested the tentative diagnosis of vascular accident with infiltration of the mediastinal tissues, perhaps due to rupture of a dissecting aneurysm.

Post-Mortem Examination.—Necropsy was strictly limited to examination of the heart in which the following changes were observed:

On opening the pericardial sac, the cavity was found to contain approximately 500 c.c. of soft, dark red, freshly clotted blood. After removal of the clot, the lining surfaces appeared roughened owing to the presence of a fine deposit of fibrin. The

heart weighed 300 grams. The epicardium was blood stained. None of the cavities was dilated. An increased amount of epicardial fat was present, particularly about the right ventricle. The right auricle appeared quite fibrous and hemorrhagic. On the anterior surface of the auricle toward the right border a somewhat S-shaped tear 2 cm. long was found, the margins of which were blood stained. The tear involved the entire thickness of the auricular wall, and a small amount of clot protruded through the opening. This area and the adjoining portion of the auricular wall were very thin and hemorrhagic, as though infiltrated by blood. (Fig. 4.) On the posterior aspect of the auricle was a large, thick, grayish, fibrous patch. The left auricle was comparatively normal. The tissues at the base of the heart were infiltrated by blood. Examined *in situ*, the mitral and tricuspid valves appeared normal. The aortic cusps were rigid and fibrous; the anterior and right posterior

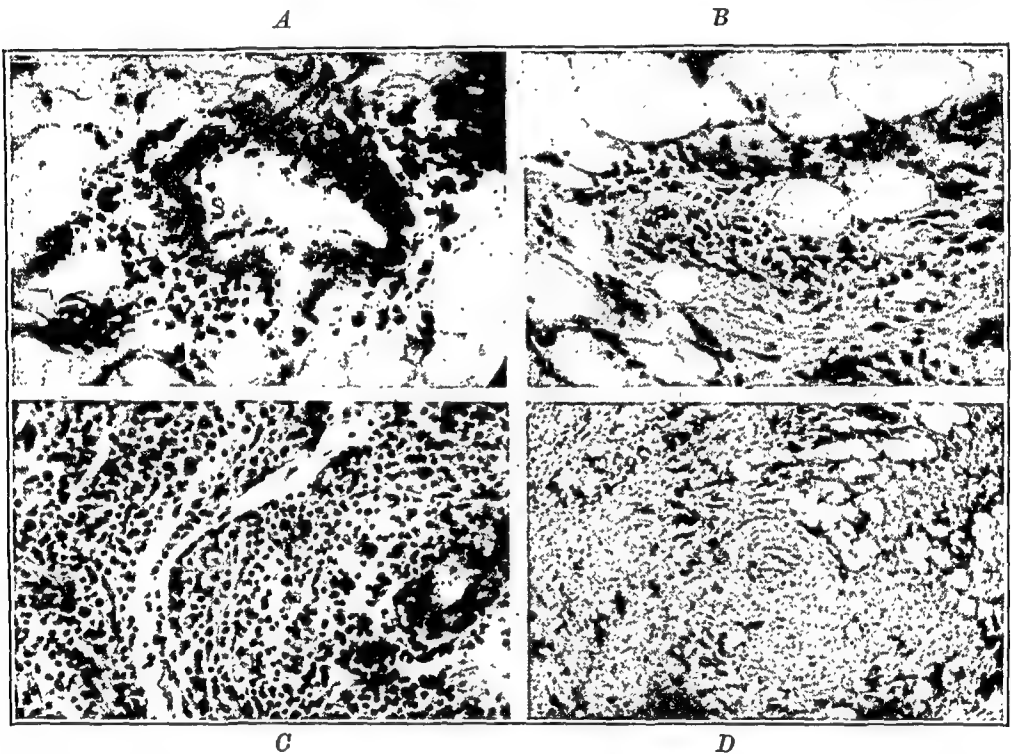


Fig. 5.—Photomicrographs of sections of the auricular wall near site of rupture. *A*, and *B*, perivascular lymphocytic infiltration; *C*, cellular infiltration containing many red blood cells; and *D*, branch of coronary artery in auricular wall showing almost complete occlusion.

cusps were firmly united by dense fibrous tissue forming a thick, reddish, elevated ridge on the upper surface of the valve. The mouths of the coronary arteries appeared small but were not occluded. The myocardium was normally thick and firm, and showed a few grayish streaks, most abundant in the interventricular septum. The coronaries appeared normal. There was no sclerosis or intimal thickening.

Microscopic sections showed evidence of disease of the coronary arteries. In the smaller branches within the ventricles there was distinct intimal thickening and fibrosis with great contraction of the lumina. The vessels of the epicardium in many instances contained completely hyalinized thrombi. There was no calcification. A few scattered patches of fibrosis were found in the myocardium and a slight general increase of intermuscular connective tissue. The epicardium contained many thick patches of fibrous tissue. In the aortic valve masses of old fibrous tissue,

largely calcified, were found. At the base of the valve distinct bone formation had occurred with osteoclasts, lacunae and a configuration simulating Haversian canal systems.

Sections of the right auricular wall near to and remote from the site of rupture showed thickening and extensive infiltration of red blood cells. A thin film of hyalinized material was present on the pericardial surface. The subpericardial tissue and muscle showed considerable disorganization due to edema and cellular infiltration. Many polymorphonuclear leucocytes were present, and these, together with other cellular elements, showed considerable karyorrhexis. Many of the small vessels showed intimal thickening, hyaline change and great contraction of the lumens. (Fig. 5.)

In the case here reported it appears that although the main coronary vessels were comparatively normal, the smaller branches were markedly altered. The prominent intimal thickening and the presence of hyaline material simulating thrombi suggest that the initial symptoms were due to infarction of the auricular wall and interstitial hemorrhage. These changes caused sufficient weakening of the wall to lead to rupture and hemopericardium.

There was no finding at autopsy to explain the difference in blood pressure noted between the right and left arms.

DISCUSSION

An analysis* of 55 cases of rupture of the auricle (54 from the literature plus the one here described), reveals certain interesting facts. Auricular rupture in contrast with ventricular, occurs more frequently at younger age periods. Thus, in 44 instances of ruptured auricle, 21 or 47.7 per cent were found in individuals under forty years. This incidence is seven times as great as that given for all ruptures of the heart, where only 6.7 per cent occur before the fortieth year.⁵ Males are more often the victims of rupture of the auricle than are females, in the proportion of 30 to 16, in 46 cases where the age was recorded. The site of rupture was as follows in 55 cases: right auricle 39, left auricle 15, and interauricular septum 2 (one case had tears both in right auricle and in septum). Trauma, either trivial or severe, was found to be a primary cause in six instances. Exertion seems rarely, if ever, to have produced the rupture, the attack developing suddenly while the patient was in bed, walking, standing or engaged in his usual activities. Rowing a boat, straining at stool or vomiting are described as preceding the onset of an attack.

The clinical picture closely resembles that of coronary occlusion. In the majority of cases, 30 out of 46, death occurs almost immediately without premonitory symptoms—the patient giving a sharp cry or groan and falling unconscious. Less frequently a longer period elapses before death, varying from an hour to seven days, during which time symptoms of severe precordial, substernal or upper abdominal pain, nausea, vomiting, dyspnea, cyanosis, clammy cold skin, rapid weak pulse, signs of heart failure and falling blood pressure may develop. The presence of fever and electrocardiographic changes described in our case have not been recorded before in the literature.

*This analysis with full bibliography will be published elsewhere at a later date.

The pathological findings in the series of 55 cases are limited for the most part to brief descriptions of the gross appearance of the heart. Hemopericardium was present in the majority of instances, absent in a few, and not mentioned in the remainder. Escape of blood into the pleural cavity is described in a few cases where the pericardium was adherent, or where rupture occurred behind the pericardium. The tear averaged about $\frac{1}{2}$ to $\frac{3}{4}$ inch in length as a rule, and the auricular wall is described as being unusually thin near the point of rupture. In the majority of reports no mention is made of the condition of the coronary arteries. In a few instances these are described as being sclerosed. There are only 9 cases in the series of 55 in which microscopic examination of the heart was made. Several of these note the presence of interstitial hemorrhage in the auricular wall, accompanied by intimal thickening of the smaller coronary artery branches, a process of obliterating endarteritis, leading to infarction of the auricular muscle.

The mechanism of rupture of the auricle, therefore, if one excludes the traumatic cases, would seem to be similar to that of rupture of the ventricle, and to be dependent upon disease of the nutrient arteries. In the former the vascular changes are largely confined to the smaller vessels in the atrial wall detectable only by microscopic examination, while in ventricular rupture changes such as extensive atheroma, narrowing or thrombosis of large coronary branches are generally visible to the naked eye. We believe that spontaneous rupture of the auricle does not occur in normal hearts if the traumatic cases be excepted, and that in the future careful histological studies, if made, will show a pre-existing obliterative endarteritis, such as has been described in the case reported above. The cause of death is not fully understood, although in the ruptures with extensive hemopericardium the increased pressure within the pericardial sac, especially if it develops quickly, is believed to produce anoxemia of the heart muscle, resulting in death. This theory has some experimental support, such as Cohnheim's tamponade investigation, but does not explain death in the instances where the pericardial cavity contains no blood.

SUMMARY

1. A case of apparently spontaneous rupture of the right auricle is reported in a supposedly normal individual where trauma and excessive exertion were absent.
2. Serial electrocardiograms in this case showing changes suggestive of coronary occlusion are presented for the first time.
3. Histological study revealed a pre-existing obliterating endarteritis with interstitial hemorrhage and infarction of the auricular wall, leading to rupture, a process essentially similar to that causing rupture of the ventricle.

4. The clinical and pathological features of rupture of the auricle based on a review of 54 cases in the literature, plus the one here described, are discussed.

5. The large incidence of rupture of the auricle before the fortieth year of life, 47.7 per cent, as against 6.7 per cent for ventricular rupture, is pointed out.

REFERENCES

1. Harvey, William: *De Circul. Sangu.*, Exercit 3, cited by Morgagni, J. B., Ref. 2. *The Seats and Causes of Diseases*, translated by Benjamin Alexander, London, 1769, Letter 27, p. 830.
2. Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, *Am. J. M. Sc.* 170: 828, 1925.
3. De la Chapelle, C. E.: Spontaneous Rupture of the Heart, *AM. HEART J.* 1: 315, 1925-26.
4. Benson, R. L., Hunter, W. C., and Manlove, C. H.: Spontaneous Rupture of the Heart, *Am. J. Path.* 9: 295, 1933.
5. Davenport, A. B.: Spontaneous Heart Rupture. A Statistical Summary, *Am. J. M. Sc.* 176: 62, 1928.
6. Lisa, J. R., and Ring, A.: A Case of Occlusion of Both Coronary Arteries With Rupture of the Auricle, *J. Lab. & Clin. Med.* 16: 1083, 1931.

CHANGES IN THE RS-T COMPONENT OF THE ELECTRO-CARDIOGRAM PRODUCED BY EXPERIMENTAL RUPTURE OF THE AURICLE OF THE DOG'S HEART AND BY PERICARDIAL INJECTION*

F. S. RANGLES, M.D.,† L. W. GORHAM, M.D., AND M. DRESBACH, M.D.
ALBANY, N. Y.

INTRODUCTION

THIS study was prompted by the occurrence of spontaneous rupture of the auricle in a patient seen in consultation by one of us (L.W.G.) in April, 1930. A report of the case has been presented in the preceding article by Clowe, Kellert, and Gorham. The outstanding feature of it was the almost exact duplication in symptomatology of coronary occlusion, and this clinical diagnosis was apparently supported by changes in the electrocardiogram presumably characteristic of such an accident. The finding post mortem of coronary arteries normal in the gross, and of a patent tear in the right auricle, together with a marked hemopericardium, suggested that the electrocardiographic changes were not in this instance diagnostic of coronary disease, but were due either to the auricular damage or to the hemopericardium. In order to determine whether or not similar changes in the electrocardiogram could be produced by experimental rupture of the auricle, these experiments were undertaken.

REVIEW OF PREVIOUS EXPERIMENTAL WORK DEALING WITH THE PRODUCTION OF RS-T CHANGES IN THE ELECTROCARDIOGRAM

In the past few years numerous papers dealing with experimental alterations in the electrocardiogram have been published, with reviews and discussions of previous work. Our discussion will be limited to the RS-T component of the cardiogram, and the literature cited will serve as a guide to practically all of the publications, in this special field, of the past decade as well as to the earlier work.‡

The literature of experimental studies on the T-wave alone had already become very extensive by 1925, as the review by Katz¹ then showed. Thomas Lewis² was apparently the first to engage in work on coronary artery ligation, with electrocardiographic controls. However, F. M. Smith³ seems to have priority in this field as far as special refer-

*From the Departments of Physiology and Medicine, Medical Department of Union University, Albany Medical College, Albany.

†Harriet Sporborg Littauer Fellow in Physiology and Research Medicine.

‡Extended recent discussions of various aspects of the problem of alteration of the electrocardiogram consequent to myocardial changes due to various conditions acting directly or indirectly on the heart can be found in the papers by Damir and Lampert, Feil and associates, Crawford and coworkers, Barnes and Mann, Katz, and others, cited in this review.

ence to the coronary type of T-wave is concerned. Using dogs, he observed that coronary ligation resulted in a T-wave form very similar to that in a proved clinical case of coronary thrombosis, which case was later described by Herrick.⁴ Smith extended his research in 1920.⁵ Ligation experiments with electrocardiographic records were later made on dogs by Sutton and King,⁶ Otto,^{7, 8} Parade,⁹ Averbuck and Rachmilewitz,¹⁰ Feil, Katz, Moore and Scott,¹¹ Damir and Lampert¹² and by Barnes and Mann.¹³ Gold, DeGraff and Edwards¹⁴ used cats in similar experiments.

There is general agreement that coronary artery ligation in dogs produces changes in the RS-T component resembling, especially in the early stages of the process, those resulting from myocardial infarction in man; but all the factors involved are not fully understood. Parade observed that by the time the coronary type of T-wave has developed the damaged area has already begun to organize. Feil and associates found that after ligation an increasing anoxemia was necessary to insure, within an hour or so, the changes in the electrocardiogram, and they concluded that coronary obstruction was only one factor. On the other hand, Barnes and Mann did not emphasize the anoxemia element but pointed out that the RS-T changes are inconstant owing to peculiarities of the arterial distribution in the dog's heart which make it difficult, if not impossible, to reproduce the late electrocardiographic changes seen in myocardial infarction in man. Katz and Wallace¹⁵ also showed the relation between clinical and experimental electrocardiograms and pointed out the errors which are likely to creep into such work. In their extensive study Damir and Lampert¹² found not only real differences between the cardiograms following cardiac infarction in man and the dog, but also features common to the two types. They likewise discussed at length the relations between the form of the electrocardiogram and infarction.

It may be mentioned at this point that in a number of cases of stab wounds of the human heart, with consequent damage or obstruction of coronary arteries, changes in the electrocardiogram have been observed which are very similar to those due to the ordinary thrombotic coronary occlusion in man and to coronary ligation in animals. Such cases have been reported by Davenport,¹⁶ Puccinelli,¹⁷ Cole,¹⁸ Bates and Talley,¹⁹ Schlomka,²⁰ Purks,²¹ Elkin and Phillips,²² and by Porter and Bigger.²³

The researches of Otto,²⁴ Averbuck and Rachmilewitz,¹⁰ McGuire²⁵ and Damir and Lampert¹² on the changes of the RS-T component caused by chemical injury of the myocardium, by cooling it, by coronary ligation, by stimulation of the cardiac sympathetic nerves and by excision of the stellate ganglia are important. Although there is some disagreement among the above mentioned and other investigators regarding the actual rôle and importance of different factors in the origin and subsequent changes in the RS-T component, the results furnish accumulat-

ing evidence that certain features, at least, of the coronary type of T-wave can be produced by a variety of means. An observation of much interest in this connection is one by Damir and Lampert¹² who found that in a number of dogs excision of the left stellate ganglion produced T-wave changes resembling certain of those produced by coronary ligation, although there was no myocardial damage. They also found that RS-T abnormalities caused by silver nitrate injury of the heart or by coronary ligation could sometimes be made to disappear by removal of the right stellate ganglion. These experiments, and some by Otto,⁷ Averbuck and Rachmilewitz,¹⁰ and McGuire,²⁵ on the extracardiac nerves, suggest an important nervous factor in the production of abnormalities of the RS-T component but leave some points obscure. Confirmation of certain of the experimental results reported is desirable.

In the past the lack of uniformity in the correlation of the RS-T changes and cardiac injury has been partly due to the technic employed. Recognizing the difficulties of confining a lesion to a definite part of the ventricles, Crawford and associates²⁶ employed the electric cautery, using the cat heart. They state that lesions in similar sites produced, with almost complete consistency, the same type of RS-T deviation. They are of the opinion that the geographical situation of the lesion, rather than the distribution of the blood supply, determines the character of the electrocardiographic changes. Nevertheless, other recent work has emphasized the importance of the arterial distribution in the heart (Otto,⁸ Parade,⁹ Barnes and Mann¹⁸).

Changes in intracardiac pressure (Otto,²⁷ Lian and Marklen²⁸) alter the RS-T complex in a suggestive way, and injections of isotonic saline solution and of oil into the pericardial sac can, by pressure, produce RS-T changes similar to those in certain stages of clinical cases of coronary occlusion (Katz, Feil and Scott,²⁹ Scherf³⁰). We have also confirmed this observation in our work, as will be noted later.

It is well known that drugs of various kinds can invert the T-wave, and not infrequently the RS-T deviations are similar to those under discussion. For this reason digitalis and other glucosides are of obvious importance. However, there is marked disagreement in the reports on these glucosidal effects in animals (Grünbaum^{31,*} DeGraff and Wible,³² and Brams and Gaberman³³). In a dozen or more experiments on cats and dogs RS-T changes somewhat similar to those of the coronary type have been seen in our laboratory. They were produced by ouabain and strophanthidin under certain conditions and will be described in a later paper.

Finally, we mention the recent work of Kountz and Grüber³⁴ and of Kountz and Hammouda³⁵ on anoxemia of the heart. The former workers found that when the oxygen content fell below 50 per cent of normal in

*The experiments of Grünbaum have to do only with changes in the electrocardiogram of man.

the arterial blood of dogs during rebreathing experiments the electrocardiogram showed changes strikingly similar to those of coronary occlusion in man. Gruber and Kountz³⁶ also showed that coronary arterial constriction produced by pitressin can provoke marked RS-T alterations. Kountz and Hammouda³⁵ have extended this work, using the heart-lung preparation, and have obtained evidence that metabolites, rather than anoxemia alone, acting locally on the myocardium are responsible for the RS-T effects, though the combined factors of deficient oxygen and excess carbon dioxide may also produce them.

It has become increasingly apparent, from both clinical and experimental work of the past ten years, that fusion of the T-wave with the RS segment of the electrocardiogram is not pathognomonic of coronary occlusion, though serial cardiograms in suspected cases furnish very suggestive evidence of such obstruction in many instances (Cooksey and Freund³⁷). From the experimental work reviewed it is evident that, apart from direct myocardial damage or necrosis by any agency mentioned, many of the procedures used to affect the ventricular musculature indirectly have, as a common result, the production of myocardial ischemia of greater or lesser degree and extent. It seems reasonably clear that although in such cases anoxemia alone is not the sole factor in producing the RS-T changes it may bring them about when associated with an excess of metabolites, as the experiments of Kountz and Hammouda³⁵ indicate. Further correlation of the results of experimental study of the RS-T portion of the electrocardiogram is desirable.

DESCRIPTION OF EXPERIMENTS

A. Auricular Rupture

Dogs were chosen as the experimental animals. Three preliminary experiments were performed in which the chest was opened under morphine and ether anesthesia and the right auricle was cut or torn to produce bleeding into the pericardial cavity, the latter being closed by a purse string suture. Electrocardiograms taken before and after this operation showed no significant changes as a result of either the auricular injury or the hemopericardium. No attempt was made in these first three experiments to preserve aseptic technic or to keep the animals alive beyond a period of a few hours.

Following the preliminary experiments a more or less standardized technic was adopted which may be described as follows:

An electrocardiogram was taken by the three standard leads, before anesthetizing the animal. It was found convenient and entirely satisfactory to use electrodes consisting of three or four turns of No. 18 copper wire wrapped about the legs of the dog after first scrubbing the hair with strong salt solution and applying about a yard of heavy web bandage two inches wide soaked in the same solution. This is the procedure recommended by Herrmann and Wilson.^{38*}

The dog was then given 40 to 50 mg. of sodium amytal per kilogram of body weight. This was given intraperitoneally and was supplemented by ether, if neces-

*The peaks of the R and S deflections, being almost invisible in most of the records, have been retouched with white ink in order to indicate the amplitude of those two waves.

sary, to produce surgical anesthesia. A second electrocardiogram was taken after anesthesia had been induced. The chest was then opened under aseptic precautions, the respiration being maintained by an air pump connected with a tracheal tube. The opening made in the chest wall was on the left side between the third and fourth or fourth and fifth ribs. A sketch showing the incision is seen in Fig. 1. The pericardium was picked up with a clamp, and a purse-string suture of fine fishline was placed about the tip of the clamp. Then through a small opening made in the pericardium inside the purse-string suture a clamp was passed back toward the base of the heart, and the right or left auricular appendage was grasped and drawn out through the opening in the pericardium. (The left auricle is easily seen through the pericardium and is much more accessible, but the right auricle was used in a majority of experiments in order to duplicate more exactly the condition present in the case of spontaneous rupture referred to above.) A curved clamp was then placed on the auricular appendage about three-eighths of an inch

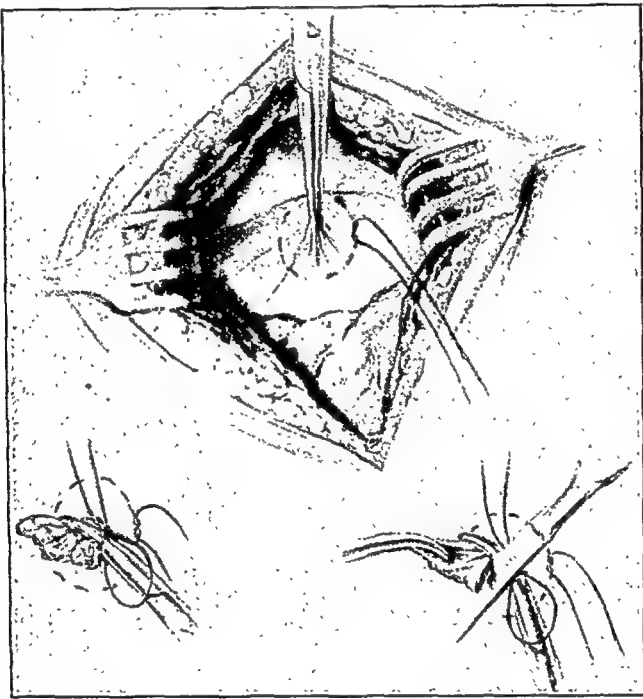


Fig. 1.—Upper: Drawing of operative field with clamp picking up pericardium and purse-string suture in place.
Lower left: Tip of auricular appendage in clamp with slip tie in place.
Lower right: Tip of auricular appendage being cut away.

from the tip. Back of the clamp was then tied a slip ligature of strong fishline drawn tight. A knot was tied in the slip end of the tie for identification and this was brought out through the chest wall. The other end was cut off close to the tie. A second fishline suture was placed through the wall of the auricle directly back of the tie and the two ends were brought outside. (The purpose of this so-called "saw string" will be described later. It was not used in all experiments but was found very important.) The tip of the auricular appendage was then cut off close to the clamp, the clamp removed carefully and the auricle allowed to slip back to its normal position within the pericardium. The purse string in the pericardium was drawn, closing the opening. The chest wall was closed by three layers of sutures, the artificial respiration was stopped, and another electrocardiogram was taken after the animal had resumed normal breathing. In one to three days after the operation, the string which controlled the slip tie on the cut auricle was

drawn out and the second ligature which had been placed in the wall of the auricle was torn out by sawing back and forth until it cut through the muscle. The use of the saw string was essential to insure free bleeding from the auricle. It had been found that the cut end of the auricular appendage was sealed by clot formation within twenty-four hours so that little or no bleeding would occur on removing the slip ligature unless the wound were freshly torn open. Electrocardiograms were taken before, during, immediately after this procedure, and at varying intervals over periods ranging from several days to two months.

Protocols of Typical Experiments.—

January 27, 1932. Experiment 18.

Dog 40, male, three and one-half months old, weight 12.6 kg. Electrocardiogram at 8:20 P.M. (3 leads), followed by sodium amytal (50 mg. per kg.), intraperitoneally. Well anesthetized at 8:50 P.M. when a second electrocardiogram was taken. Operated upon as described above, removing the tip of the right auricular appendage. No bleeding. Purse string drawn in pericardium; chest closed and bandaged. Very little ether was required. Dog appeared in good condition. Third electrocardiogram taken.

January 28. 9 A.M. Animal somewhat under the influence of amytal but tried to stand. Drank water.

January 28. 4 P.M. Dog able to walk. Electrocardiogram taken at 4:15 P.M. Bandage removed and incision opened at one end to locate buried strings. "Slip string" pulled at 4:35 P.M. followed immediately by the "saw string." Electrocardiogram taken at once and another after ten minutes. Animal in good condition.

January 29. Dog active and apparently normal. Electrocardiogram at 11:30 A.M.

Further electrocardiograms were taken as follows: January 30 and 31. February 1, 2, 3, 4, 6, 9, 15, 19, and 29.

Electrocardiographic Changes.—The electrocardiogram taken January 27 before operation is shown in Fig. 2. It is a perfectly normal tracing but the rate is fairly rapid. The records taken immediately following the operation show no change of any consequence. The first marked variation appears in the tracing taken January 29 at 11:30 A.M., nineteen hours after pulling the string to produce hemorrhage into the pericardium. This record is shown in Fig. 3. Here is found sharp inversion of T-waves in Leads I and II with decided elevation of the S-T interval. The T-waves take off 1-2 mm. above the base line, and the S-T line is definitely convex upward. The next day the T-waves are upright in all leads, but the take-off remains high. Fig. 4 shows the record obtained February 6, nine days after pulling the string. Here we find very high T-waves, especially in Lead II, and a high take-off in all leads. From this time on repeated tracings showed a gradual return to normal. On February 29 the last record was taken. This is reproduced in Fig. 5, and except for a slight elevation of the S-T interval, it is seen to be practically the same as the original tracing taken before operation. Consequently this dog was used again for a second experiment which is next described.

February 29, 1932. Experiment 23.

Dog 40, male, four and one-half months old, weight 15.3 kg. This dog was first operated upon January 27, the tip of the right auricle being cut away at that time. The second operation was exactly the same as the first except that the tip of the left auricle was removed. Electrocardiograms taken. Animal in good condition.

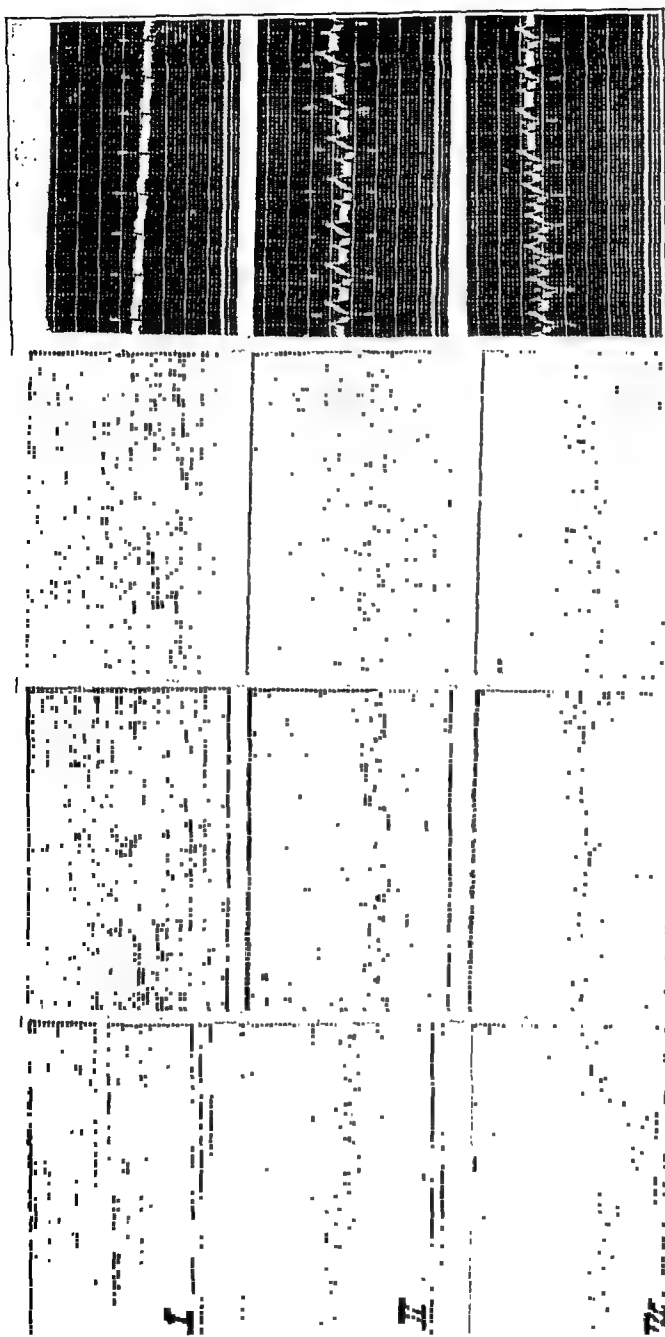


Fig. 4.

Fig. 2.—Experiment 18, Dog 40. Before operation.

Fig. 3.—Nineteen hours after pulling string. Note inversion and high take-off of T₁ and T₂. A-V block in Lead II.

Fig. 4.—Nine days after pulling string. Note high T₁ waves with high take-off.

Fig. 5.—Thirty-two days pulling string. Note return to near normal. This serves as control for Exp. 23 in which dog was again operated upon.

March 1. 9 A.M., Dog lying on side still under effect of amytal. 1 P.M., Animal able to walk about. 1:15 P.M., Electrocardiogram. 2:05 P.M., Slip string pulled, followed by "saw string." Electrocardiogram taken during and after pulling string. 5 P.M., Electrocardiogram.

March 2. 9 A.M., Dog up and about but not active. Some infection around

sutures. 10:30 A.M., Electrocardiogram. This showed a return of the characteristic changes in the form and take-off of the T-waves in all leads. Therefore, at 2:30 P.M. the same day, the dog was again anesthetized and the heart exposed through the original incision to determine the amount of blood in the pericardium. The latter was found greatly distended with fluid. By means of a syringe and needle 90 c.c. of dark red bloody fluid were removed from the pericardial sac besides about 20 c.c. which were lost by leakage around the needle. Chest again closed and an electrocardiogram taken. Dog in fair condition.

March 3. 9 A.M., Dog moved about, but was not active. 10:45 A.M., Electrocardiogram. Repeated at 3:20 P.M. The dog was then sacrificed and an autopsy done. The left lung was found adherent to the chest wall and to the pericardium. The latter was thickened, injected and very friable. Bloody fluid oozed from the opening made by the needle used the day before for aspiration. The pleural cavity contained 72 c.c. of bloody fluid, part of which had leaked from the pericardium. The pericardial sac contained 42 c.c. of similar material. No adhesions between pericardium and heart wall. Right auricular appendage missing and wound fully healed. Left auricular appendage also missing and wound closed by mass of fibrin. Opening not patent but on pressure blood was forced out from left auricle.

Electrocardiographic Changes.—Three hours after pulling the string, the characteristic changes in the form and take-off of the T-wave begin to appear in Lead I. The electrocardiographic record before operation is seen in Fig. 5, and the record taken three hours after producing hemorrhage into the pericardium is shown in Fig. 6. Twenty hours after producing a hemopericardium the changes are more pronounced as shown in Fig. 7. Here the T-waves are inverted in all leads, and the take-off is elevated in Leads I and II. Four hours later the T-wave in Lead III is found upright, but otherwise the picture is essentially the same (Fig. 8). Following the removal of bloody fluid from the pericardium by aspiration T_s becomes inverted again, and now in all leads we find inverted T-waves and a high take-off (Fig. 9). Nineteen hours after removing the blood from the pericardial sac, the changes are even more pronounced (Fig. 10). The T-waves are still inverted in all leads, and the take-off is higher than before.

The interesting point in this experiment is the fact that it was the second time that such electrocardiographic changes had been produced in the same dog by a second auricular rupture and a consequent hemopericardium. Of further interest is the fact that these changes not only persisted but were intensified after removal of a large part of the blood from the pericardium. It would appear that these changes were evidence of a myocardial disturbance which persisted after release of pressure within the pericardial sac.

Review of Auricular Rupture Experiments.—The series comprised in all, 18 experiments on 16 dogs. The right auricle was opened in eleven instances, the left in seven. Definite electrocardiographic changes were obtained in eight experiments, or 44.4 per cent. The right auricle was opened in five of these and the left in three. However, in only eleven of the eighteen experiments did the dogs survive the operation for twelve hours or longer. In other words, there were only eleven instances in

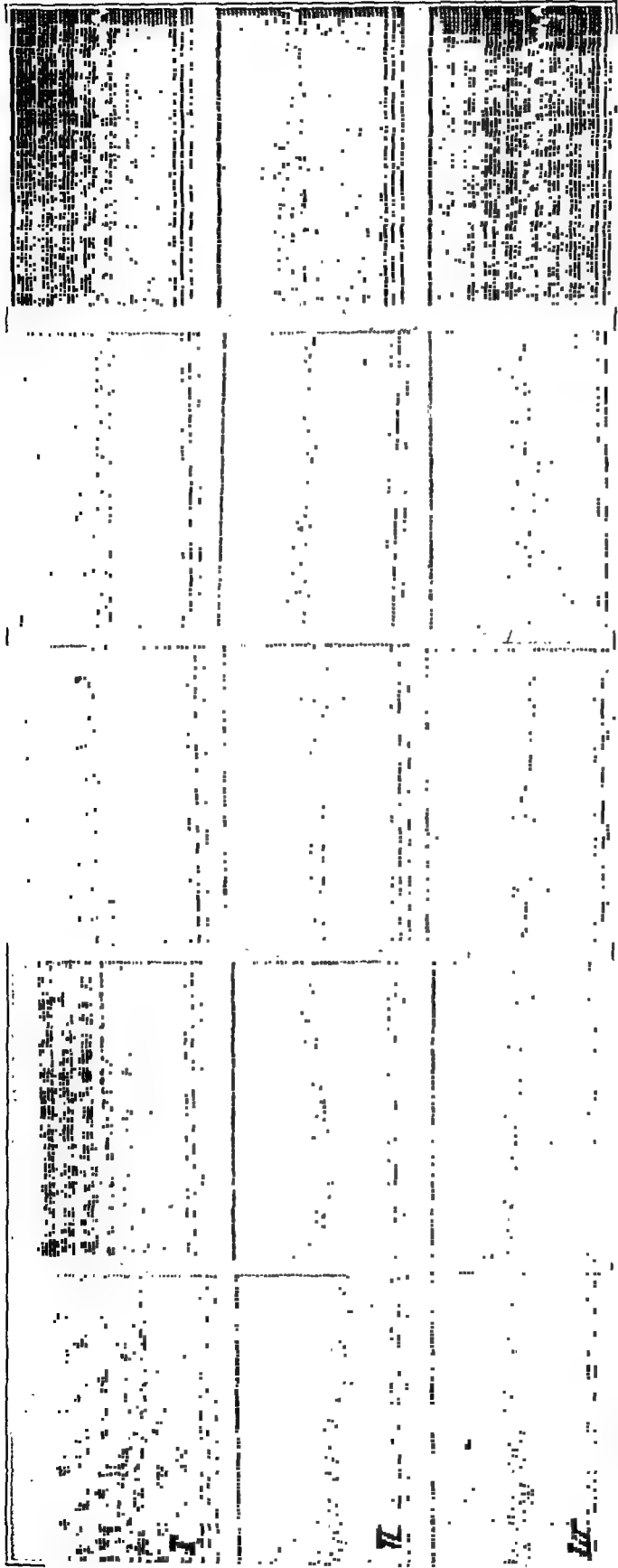


Fig. 6.—Experiment 23, Dog 40. Three hours after pulling string. Note inversion and high take-off of T_1 . Compare Fig. 5.
Fig. 7.—Twenty hours after pulling string. All T -waves now inverted with ST interval elevated and convex upward.
Fig. 8.—Twenty-four hours after pulling string and just before removing blood from pericardium. T_3 upright.
Fig. 9.—Immediately after removing 90 c.c. of blood from pericardium. T_3 again inverted. High take-off in all leads.
Fig. 10.—Nineteen hours after removing 90 c.c. of blood from pericardium. Note extremely high take-off and persistent inversion of T -wave.

which the animals lived a sufficient time for electrocardiographic changes to develop. Of this number eight showed the alterations that have been described above, a percentage of 72.7. In three cases no changes could be detected. Of this number two experiments were on the same dog. No "saw string" was used in either to insure opening the auricular wound, and it is probable that no appreciable hemorrhage into the pericardium occurred. Autopsy three days following the second experiment on this animal showed no evidence of bleeding from the auricle into the pericardium. The other failure was in the first experiment of this series. In this case the electrocardiograms were not taken at the right time and only one lead was used.

In seven dogs death occurred within twelve hours after operation. The causes of death in these cases were determined as follows:

Failure of slip ligature to hold, four; prolonged operation and anoxemia, one; pulmonary embolism, one; slip string pulled too soon (fifteen minutes) after closing chest, one.

Survival Period.—Of the eleven experiments in which the dogs lived more than twelve hours, the survival period was from three to sixty-four days. All animals were sacrificed eventually except one which developed a severe wound infection with a pyopneumothorax resulting in death on the sixth day after operation.

Use of "Saw String."—The importance of the "saw string" to insure bleeding cannot be overemphasized. The healing process was apparently so rapid and the intra-auricular pressure so low that there was little likelihood of bleeding from the cut auricle unless the wound was re-opened. Simply untying the ligature was not enough to tear apart the edges of the cut auricle after healing had gone on for twenty-four hours or longer. This was accomplished readily by the use of the "saw string." In no case where this means was used to insure bleeding, and in which the dog survived the operation, did electrocardiographic changes fail to develop.

Blood Pressure in the Brachial Arteries.—Since one of the striking features of the clinical case of spontaneous auricular rupture previously mentioned was the difference in blood pressure in the two arms, this point was investigated in the experimental series. Blood pressure in both brachial arteries was recorded by means of a mercury manometer in three animals with experimental auricular rupture showing definite electrocardiographic changes. The pressure was found to be the same on the two sides in every case and within normal limits.

B. Pericardial Injection

In this series of experiments it was decided to introduce blood and other fluids into the pericardial cavity by means of a needle, thus eliminating direct mechanical injury to the auricular wall. The technic of this operation was as follows:

An electrocardiogram was taken and the dog was anesthetized with sodium amytal and ether. The chest was opened in the same way as previously described. The pericardium was picked up at a point on the left side about midway between the base and the apex. A very small needle hole was made, just large enough to allow the edges to be grasped by two mosquito clamps. A short blunt hypodermic needle, No. 20, was introduced through the opening and the edges were drawn out along the needle by means of the small clamps. Then a strong fishline tie was placed about the conical projection of the pericardium along the needle, and this ligature was drawn tight about the needle. The fluid, warmed to 39° C., was then introduced by means of gravity or a large syringe until the desired amount had been used. The tie was then drawn tight on the needle by one operator while another slowly withdrew the needle from the pericardium. In this way the opening was tied off completely without leaving needle holes from which the fluid might leak. The chest was then closed, an electrocardiogram was taken at once, and repeated once or twice daily during survival of the animal. A typical experiment of this series is described below.

Protocol of Typical Experiment.—

January 11, 1932. Experiment 15.

Dog 37, female, weight 12.8 kg. An electrocardiogram was taken and the dog anesthetized with sodium amytal (50 mg. per kg.) intraperitoneally. After another electrocardiogram, the chest was opened and a No. 20 blunt hypodermic needle was tied into the pericardium as described above. Seventy cubic centimeters of blood serum obtained from another dog were then slowly introduced. This produced a weak heart beat, and it was feared that more pressure would kill the animal. The pericardium was tied off as the needle was withdrawn and no leak developed. Chest was closed and the dog began breathing. Another electrocardiogram was taken, and the animal was placed in cage still under deep anesthesia. Condition did not appear to be good.

January 12. 9 A.M., Dog lay flat on side, still under effect of amytal. Breathing somewhat labored. 10:30 A.M., Electrocardiogram. 5:30 P.M., Animal still lay flat on side. Drank water when aroused. Not able to stand.

January 13. 9 A.M., Animal stood up but did not move about. Drank water but refused food. 10 A.M., Electrocardiogram. 8:45 P.M., Electrocardiogram. Condition less favorable.

January 14. 9 A.M. Dog died. At autopsy many adhesions found in left pleural cavity with some bloody fluid and small amount of pus. Left lung partly collapsed and adherent to chest wall and pericardium, which was thick and injected. Opening made at operation was fully closed and no evidence of leakage of injected fluid. About 20 c.c. of bloody fluid found in pericardial sac. Surface of heart smooth and no adhesions between heart wall and pericardium.

Electrocardiographic Changes.—The first electrocardiogram taken after the injection of fluid showed very little change. The amplitude of the QRS had decreased, and there was a slight notching of the T-wave in Lead II and Lead III. Otherwise the picture was essentially the same as before operation. This was also true of the record taken thirteen hours after injection of the fluid. However, in thirty-seven hours a definite alteration was seen. T-waves were inverted in all leads, and the S-T interval was elevated and markedly convex upward (Fig. 11).

Review of Injection Experiments.—There were six experiments in this series, three of which were successful in that the animals survived for

more than twelve hours after operation. In all three electrocardiographic changes similar to those described were noted. The animals that died soon after operation showed no significant alteration in the electrocardiogram within the short time that elapsed before death.

The fluids used for injection were dog serum, olive oil, normal saline, and dog's blood kept fluid by the addition of heparin. The amounts used varied from 60 to 128 c.c., the largest volume employed without producing the animal's death being 90 c.c. Significant electrocardiograms were obtained in one animal after the injection of only 60 c.c.

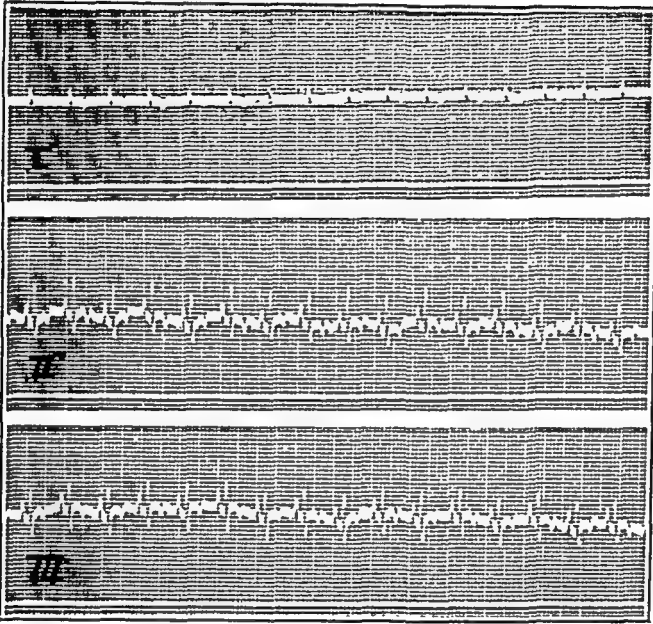


Fig. 11.—Exp. 15, Dog 37. Thirty-seven hours after injection of 70 c.c. of dog serum into pericardial sac. Note abnormal T-waves in all leads.

SUMMARY AND CONCLUSIONS

1. Experiments have been here described for the first time showing that alterations in the RS-T component of the electrocardiogram simulating those associated with coronary occlusion may be produced by experimental auricular rupture with resulting hemopericardium.

2. These electrocardiographic changes have not been found immediately after producing a hemopericardium but only following a time interval of several hours.

3. The changes have been observed to persist for some time after the absorption or withdrawal of the fluid from the pericardial sac.

4. The variations in the RS-T component were not due to the auricular injury but were associated with considerable amounts of fluid in the pericardial cavity.

5. The complete explanation of the mechanism of the production of the electrocardiographic changes in our experiments cannot be given, although the development of anoxemia as previously discussed may well be a most important factor.

6. Another method of producing RS-T changes in the electrocardiogram has been reported which adds to the existing evidence that the so-called coronary T-wave is not pathognomonic of coronary occlusion.

We desire to express our thanks to Miss Dorothy E. Chatfield, of the Albany Hospital, for assistance in the technical part of the experiments.

REFERENCES

1. Katz, L. N.: The Significance of the T-wave in the Electrogram and Electrocardiogram, *Physiol. Rev.* 8: 447, 1928.
2. Lewis, Thomas: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* 1: 98, 1909.
3. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
4. Herrick, J. B.: Thrombosis of the Coronary Arteries, *J. A. M. A.* 72: 387, 1919.
5. Smith, F. M.: Further Studies on the T-wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, *Arch. Int. Med.* 25: 673, 1920.
6. Sutton, D. C., and King, W. W.: Physiological Effects of Temporary Occlusion of the Coronary Vessels, *Proc. Soc. Exper. Biol. & Med.* 25: 842, 1928.
7. Otto, H. L.: The Extracardial Nerves. IV. An Experimental Study of Coronary Obstruction, *AM. HEART J.* 4: 64, 1928.
8. Idem: The Effect of Obstruction of the Coronary Arteries Upon the T-wave of the Electrocardiogram, *AM. HEART J.* 4: 346, 1929.
9. Parade, G. W.: Experimentelle Untersuchungen zur Frage der Koronarunterbindung, *Arch. f. exp. Pathol. u. Pharmacol.* 163: 243, 1931.
10. Averbuck, S. H., and Rachmilewitz, M.: Elektrokardiographische Studien nach Unterbindung von Coronargefässen, *Ztschr. ges. exp. Med.* 75: 562, 1931.
11. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, *AM. HEART J.* 6: 522, 1931.
12. Damir, A., and Lampert, F.: Veränderungen des Elektrokardiograms nach Unterbindung verschiedener Coronararterien zweige, *Ztschr. ges. exp. Med.* 80: 753, 1932.
13. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
14. Gold, Harry, DeGraff, A. C., and Edwards, D. J.: On the R-T Interval in Experimental Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* 23: 664, 1926.
15. Katz, L. N., and Wallace, A. W.: The Rôle of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram, *Am. J. M. Sc.* 181: ser. 2: 836, 1931.
16. Davenport, G. L.: Suture of Wound of the Heart, *J. A. M. A.* 82: 1840, 1924.
17. Puccinelli, V.: Ferita del cuore (orecchietta destra) (Wound of the heart; right auricle), *Arch. Ital. di Chir.* 14: 580, 1925.
18. Cole, W. H.: Suture of Wounds of the Heart, *Ann. Surg.* 85: 647, 1927.
19. Bates, Wm., and Talley, J. E.: The Electrocardiograms of Coronary Occlusion Following a Stab Wound of the Heart, *AM. HEART J.* 5: 232, 1929.
20. Schlomka, G.: Elektrokardiographische Beobachtungen bei Herzstichverletzung, *Deutsche med. Wchnschr.* 57: 630, 1931.
21. Purks, W. K.: The Electrocardiographic Findings Following Ligation of Descending Branch of the Left Coronary Artery in Man, *AM. HEART J.* 7: 101, 1931.
22. Elkin, D. C., and Phillips, H. S.: Stab Wound of the Heart: Electrocardiographic Study of Two Cases, *J. Thorac. Surg.* 1: 113, 1931.
23. Porter, W. B., and Bigger, I. A.: Nonfatal Stab Wounds of the Ventricles, *Am. J. M. Sc.* 184: 799, 1932.

24. Otto, H. L.: The Ventricular Electrocardiogram, *Arch. Int. Med.* 43: 335, 1929.
25. McGuire, Johnson: Der Einfluss der Nervi accelerantes auf die Herztätigkeit mit besonderer Berücksichtigung des Elektrokardiograms, *Ztschr. ges. exp. Med.* 77: 188, 1931.
26. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *AM. HEART J.* 7: 627, 1933.
27. Otto, H. L.: The Effect of a Sudden Increase in Intracardial Pressure Upon the Form of the T-wave of the Electrocardiogram, *J. Lab. & Clin. Med.* 14: 643, 1929.
28. Lian, C., and Merklen, F. P.: Alterations experimentales des portions moyenne et terminale du complexe ventriculaire electrocardiographique (compression de l'artère pulmonaire), *Compt. rend. Soc. de biol.* 107: 699, 1931.
29. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion. II. Experimental, *AM. HEART J.* 5: 77, 1929.
30. Scherf, D.: Ein Elektrokardiographisches Zeichen bei Erguss im Herzbeutel, *Wien. klin. Wchnschr.* 43: 298, 1930.
31. Grünbaum, F.: Elektrokardiographische Untersuchungen über Wirksamkeit verschiedener Digitalispräparate; ein Vergleich klinischer und pharmacologischer Wertigkeit, *Ztschr. klin. Med.* 120: 415, 1932.
32. DeGraff, A. C., and Wible, C. L.: Production by Digitalis of T-wave Changes Similar to Those of Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* 24: 1, 1926.
33. Brams, W. A., and Gaberman, Peter: The Effect of Digitalis on the T-wave of the Electrocardiogram. An Experimental Study in Human Beings, *AM. HEART J.* 6: 804, 1931.
34. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
35. Kountz, W. B., and Hammouda, M.: The Effect of Asphyxia and of Anoxemia on the Electrocardiogram, *AM. HEART J.* 8: 259, 1932.
36. Gruber, C. M., and Kountz, W. B.: The Electrocardiogram of Nonanesthetized Dogs as Modified by the Intravenous Injection of Pitressin, Atropine Sulphate and Vagus Section, *J. Pharm. & Exp. Therap.* 40: 253, 1930.
37. Cooksey, W. B., and Freund, H. A.: Serial Electrocardiographic Studies in Coronary Thrombosis, *AM. HEART J.* 6: 608, 1931.
38. Herrmann, G. R., and Wilson, F. N.: A New Electrode for Clinical and Experimental Electrocardiography, *AM. HEART J.* 1: 3, 1925.

THE RELATION OF THE INTRAPLEURAL PRESSURE TO THE MECHANICS OF THE CIRCULATION*

G. KENNETH COONSE, M.D., AND OTTO ELMO AUFRANC, A.B.
BOSTON, MASS.

IN A PRECEDING report of experimental studies we showed that there was an abnormally negative intrapleural pressure associated with experimental pneumonia, or with obstruction of the trachea or bronchi.

We observed at this time that obstruction of the trachea from within or without produced important effects on the filling and function of the heart, i.e., dilatation, cyanosis, anoxemia of the tissues, and changes in blood pressure and heart rate. It was further noted that injection of suitable intrapleural fluid exerted a definite beneficial action on both the pulmonic and general circulation in experimental pneumonia or conditions associated with partial obstruction of the trachea or bronchi.

In this paper we wish to report additional observations on the effects produced on the heart and circulation by variations of negative intrapleural pressure. It was our purpose to determine, if possible, the mechanical effects produced by alterations of the intrapleural pressure both in the systemic or general circulation, and in the pulmonic or lesser circulation. The augmented negative pressure changes were produced by decreasing the inspiratory volume. This was accomplished by increasing degrees of tracheal obstruction. The diminished intrapleural pressure effects were produced by increasing the size of the tracheal opening. The respiratory volume was controlled by means of a specially devised tracheal tube (Fig. 1).

The mechanism by means of which the normal alterations in intrapleural pressure are produced is relatively simple when the anatomy and physiology of respiration are carefully analyzed. The relation of the heart to the lungs, and the lungs to the intrapleural spaces, from a study of cross- and sagittal sections can be readily appreciated (Fig. 2). It is obvious that changes of pressure in the intrapleural spaces must of necessity affect the filling and function of the heart. If the intrapleural pressure be rendered more negative, the inflow of blood into the right heart will be greater in a given period of time, i.e., during inspiration. It is chiefly this reduced pressure effect upon the heart and great veins which enables blood to flow upward from the more dependent portions, particularly the lower extremities, against gravity. To be sure, blood from the superior vena cava in the upright position will

*From the Laboratory of Surgical Research, Harvard Medical School, Boston, Mass.

flow readily downward in its return to the right heart due to gravity, but in the prone position there will be relatively little difference from a theoretical point of view between the blood flow in the superior and inferior vena cava, as in this latter instance gravity affects both, approximately equally.

It is our belief that the rate of blood flow through the pulmonary circuit is largely determined by the intrapleural and intra-alveolar pres-

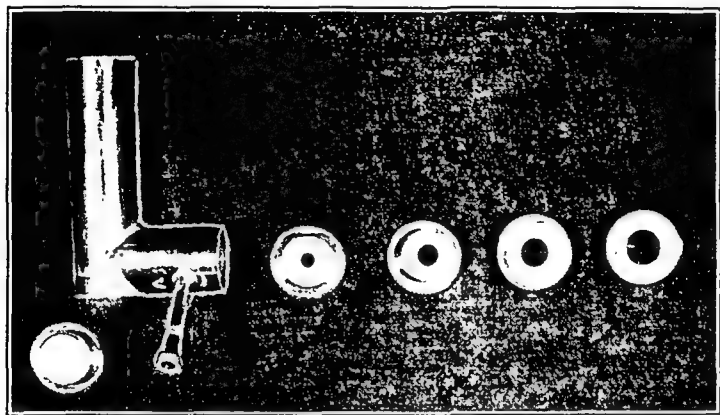


Fig. 1.—Tracheal cannula. Different sized stops may be screwed in the top of the cannula to control the volume of air entering or leaving the lungs. By means of the side arm, it is possible to measure the pressure within the trachea and bronchi by connecting it with a recording manometer.



Fig. 2.—Transverse section of thorax. Note pleural reflections in relation to the heart. Since each intrapleural space is a closed cavity, a reduction in pressure in any portion of the space will affect all parts approximately equally. It can be readily seen that a reduction in pressure in the intrapleural spaces will tend to increase the volume or dilate the heart.

ures. When the intrapleural and intra-alveolar pressures are greatly reduced, the rate of flow is diminished, and when these are less negative than normal the rapidity of flow through the pulmonary circuit is increased. The normal average rate of flow through the lungs depends upon a proper balance between the negative intrapleural and reduced intra-alveolar pressures. The mechanism for this, we believe to be as

follows: As the chest wall is lifted by muscle action, the two sides of the diaphragm descend synchronously. This constitutes a normal inspiration. At the very beginning of inspiration the chest wall and diaphragm begin to move away from the lungs. As the weight of the lung rests largely upon the diaphragm, the separation will probably not be as great between the lung and diaphragm as between the lung and chest wall in the upright position. As soon as the reduction in pressure created by the increased size of the intrapleural spaces becomes equal

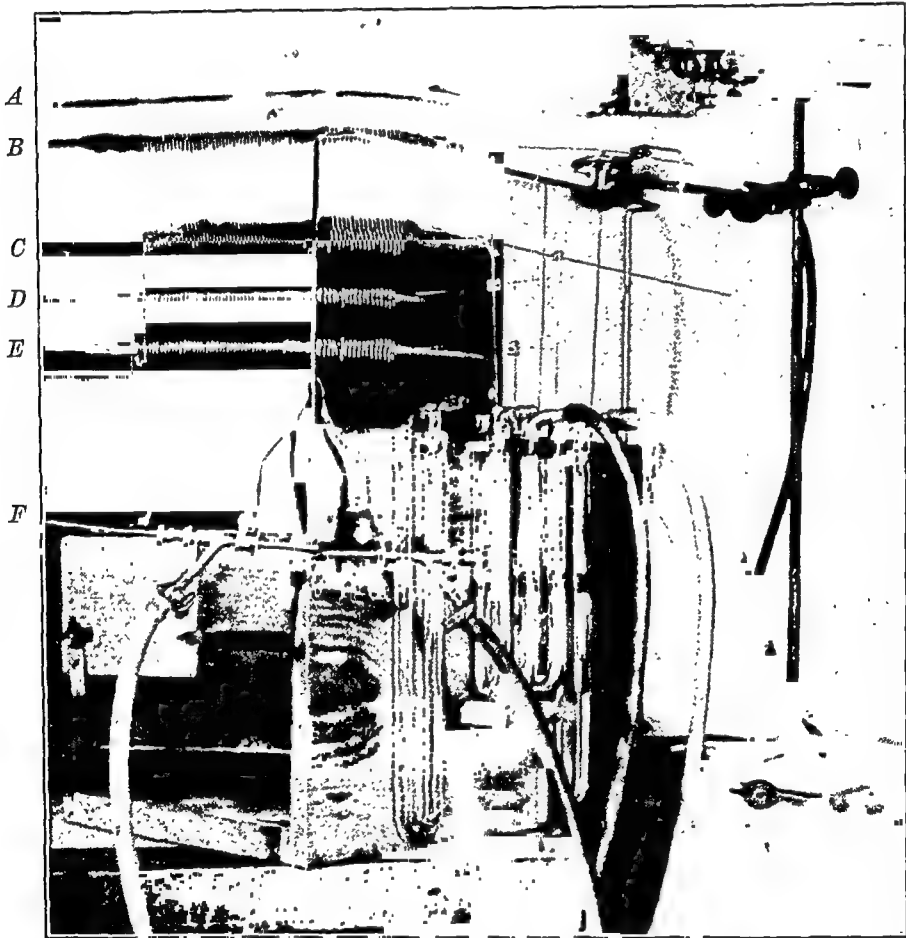


Fig. 3.—Apparatus used for recording intrapleural pressure, blood pressure, and excursions of the chest wall. *A*, time intervals; *B*, excursions of the chest wall; *C*, blood pressure tracing; *D* and *E*, intrapleural pressures; *F*, shows intrapleural needles and mechanism for holding them in place at any given distance within the intrapleural spaces. The U-tubes contain mercury with recording floats. Note the increased pulse pressure with increased negative intrapleural pressure.

to, or greater than, the elasticity and weight of the lung, the lung suddenly moves downward and outward to follow the movement of the chest wall and diaphragm. Due to the relatively small size of the tracheal opening (epiglottis) and the openings of the nose and throat (nasopharynx) a reduced pressure is developed during inspiration within the trachea, bronchi, and the alveoli. This reduction in pressure insures an adequate volume flow of blood to the lungs during inspiration. In ex-

piration the weight of the chest wall and the upward thrust of the diaphragm create a positive pressure within the alveoli, bronchi, trachea, and upper air passages, although the intrapleural pressure may still remain somewhat negative. This later observation can be explained only by assuming that the lungs do not completely fill the intrapleural spaces even during expiration (due to stretching of elastic tissue fibers within the lung). Furthermore, it must be assumed that gases are continually being absorbed from these spaces, thus keeping the pressure always sub-atmospheric. A positive pressure is essential within the lungs during expiration to facilitate removal of the accumulative waste products within the alveoli, particularly carbon dioxide, and also to insure proper

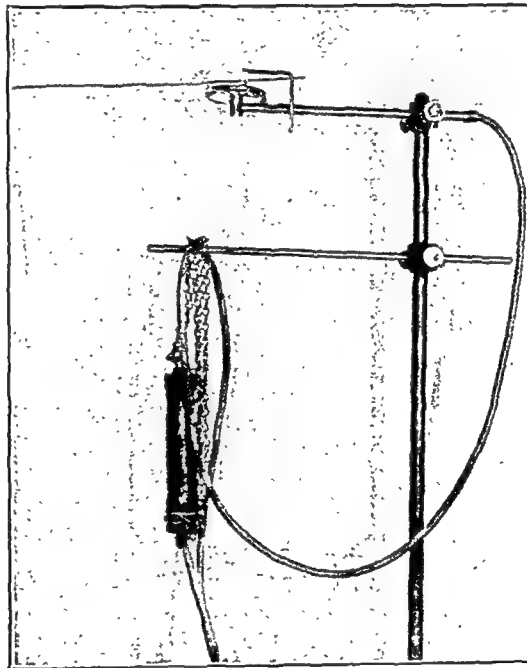


Fig. 4.—Apparatus for recording excursions of the chest wall. With inspiration the spring is elongated producing a reduction of air pressure in the closed system. These changes are transmitted to a recording tambour by means of a rubber tube connected to the side arm of the apparatus.

filling of the left auricle with oxygenated blood by compression and squeezing action. That these changes in pressure within the intrapleural spaces and lungs are of great physiological importance we have been able to demonstrate in the experimental animal.

THE EXPERIMENTAL METHOD

Healthy adult dogs were used as subjects for the experiments. Ether was chosen as an anesthetic, and a constant depth of anesthesia was maintained by the use of a standard gas-oxygen-ether machine. Bilateral intrapleural pressures were recorded on a smoked drum by connecting the needles within the pleural cavity to mercury columns (Fig. 3).

The excursions of the chest wall were recorded by means of a rubber covered spring and tambour (Fig. 4). The carotid artery was isolated, and a cannula was inserted which had been previously filled with a saturated sodium citrate solution; and this in turn was connected with the recording mercury column. The trachea was opened and the modified tracheal-cannula inserted. The trachea was then tied tightly about this so that all air entering or leaving the lungs passed through the cannular opening. By means of openings of various sizes it was possible to control the volume of air passing in and out of the lungs with each respiration. X-ray plates were taken in a number of the experiments without changing the position of the animal or the x-ray tube. In this way it was possible to record graphically alterations in the size of the heart that occurred during the experimental procedures.

We had previously noted variations of the venous pressure in our early experimental work. Many times the ordinary methods for visualization proved unreliable. A new type of venous pressure recording apparatus was devised to record graphically the rise and fall of pressure in the veins (Fig. 5). This consisted of

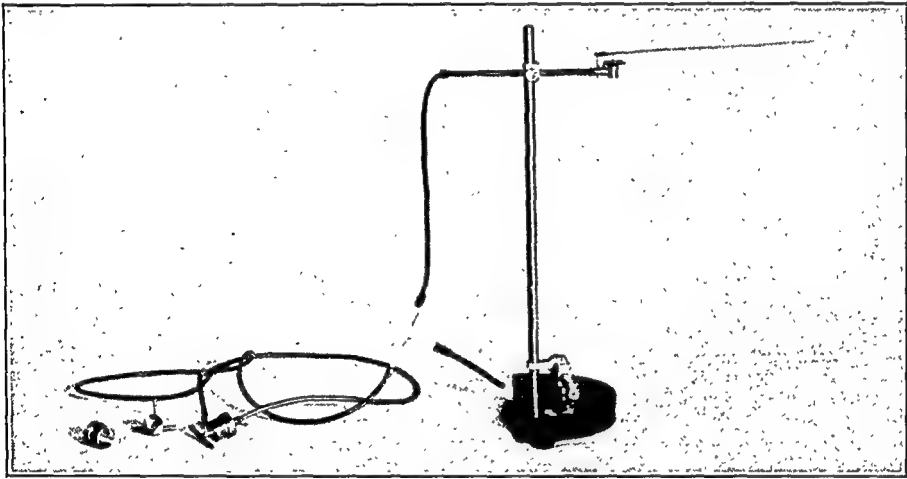


Fig. 5.—Venous recording apparatus. A thin rubber diaphragm is tied securely over the bowl. The upper portion is then screwed in place. The rubber tube and upper portion of the bowl is filled with Ringer's solution. The pressure changes are transmitted to the recording arm of the tambour.

a T-tube with a superimposed bowl which when correctly inserted lies parallel to the vein. The effects of gravity are thus largely eliminated. The tube is approximately the same caliber as the vein into which it is to be inserted. The bowl unscrews in the center and is covered by a rubber diaphragm. The surface of this is greased, and the upper portion of the bowl is screwed in place, filled with Ringer's solution, and connected to a recording diaphragm at approximately the same level as the femoral vein. A thin coat of paraffin is applied to the lower portion of the apparatus, i.e., that which comes in actual contact with the blood. This is necessary to prevent too early clotting. Any increase of pressure will thus produce bulging of the diaphragm and the pressure change will be transmitted to the fluid column of the recording diaphragm. When the pressure is reduced in the vein, blood flows out of the bowl, and the diaphragm becomes concave. The fluid column thus falls correspondingly and the change is recorded graphically on the smoked drum. The only difficulty we have encountered with this type of venous pressure recording apparatus is clotting of the blood, resulting from the slow flow produced in some of the experiments. There is a small sidearm to the instru-

ment through which Ringer's solution or saline can be injected to wash out clotted blood. In most instances this obviated the necessity of removing the apparatus from the vein.

The time intervals during the experiment were recorded by means of the usual clock mechanism and are marked on the drum at intervals of every five seconds. The heart rate was recorded in two different ways. Each systolic pulsation was recorded on the blood pressure tracing, and when the speed of the drum was increased it was possible to determine the rate, knowing the elapsed interval of time. The pulse rate was also recorded at ten- to fifteen-minute intervals by direct palpation of the femoral pulse. The rectal temperature was also taken at corresponding intervals and marked on the drum at the appropriate point.

Two general series of experiments were undertaken, first, a series with an abnormally increased negative pressure; and second, a series with a diminished negative pressure. In most instances, however, both experiments were performed on the same animal except where the experiment was allowed to go on to fatal termination. In some cases fluid was injected into the intrapleural spaces before beginning the experiment. The pressure was frequently recorded within the trachea in addition to the intrapleural pressure. The protocol of two typical experiments will serve to illustrate the method used.

PROTOCOLS

Dog 1.—An adult mongrel Police dog weighing twenty-one kilograms. Estimated age two years. Excellent general condition. Ether anesthesia. Intrapleural measurements, chest excursions, blood pressure, venous pressure, and intratracheal pressure were recorded on a smoked drum as previously described.

During the excitatory phase the negative intrapleural pressure was greatly increased, i.e., rendered more negative. As the stage of surgical anesthesia was reached, the intrapleural pressure became much less negative. With deep anesthesia it was correspondingly diminished. The blood pressure fell, venous pressure rose, and the pulse rate increased. Then the stage of poisoning was reached, and respirations ceased for two minutes. During the first ten seconds of this period the blood pressure fell fifteen millimeters and the venous pressure rose. The fall of blood pressure was followed in about one and one-half to two minutes by a rise of thirty-two millimeters. The blood pressure then gradually returned to the original normal level shortly after spontaneous respirations were resumed (Fig. 6).

A one-eighth inch stop was immediately inserted into the tracheal cannula, and the negative intrapleural pressure was at once increased to minus fifteen millimeters. Blood pressure was elevated, venous pressure at first fell, then rose slightly (Fig. 6), respirations slowed, and the heart became slow and irregular. In four minutes respirations ceased. Blood pressure promptly fell, although the heart continued to contract feebly. Venous pressure rose, then fell as the heart stopped two minutes later.

Post-mortem Findings.—Autopsy showed marked dilatation of the heart and great veins within the thorax as well as congestion of all the large veins within the abdomen. There was considerable congestion within the mesenteric vessels, with marked cyanosis, and in some instances areas of gross hemorrhage were visible. The lungs showed cyanosis and marked congestion, and the cut surface exuded dark red blood. There was some edema present but no definite pneumonia. This congestion was most marked in the bases but was also present throughout the

lungs. The liver bled freely when sectioned as did also the kidney. The venous pressure was apparently high in the vena cava. All of the superficial vessels were congested and this was particularly noted in opening the thorax.

Dog 2.—An adult mongrel dog weighing fifteen kilograms. Good general condition. Estimated age two to three years. Ether anesthesia. Intrapleural pressure, intratracheal pressure, blood pressure, venous pressure, and excursions of the chest

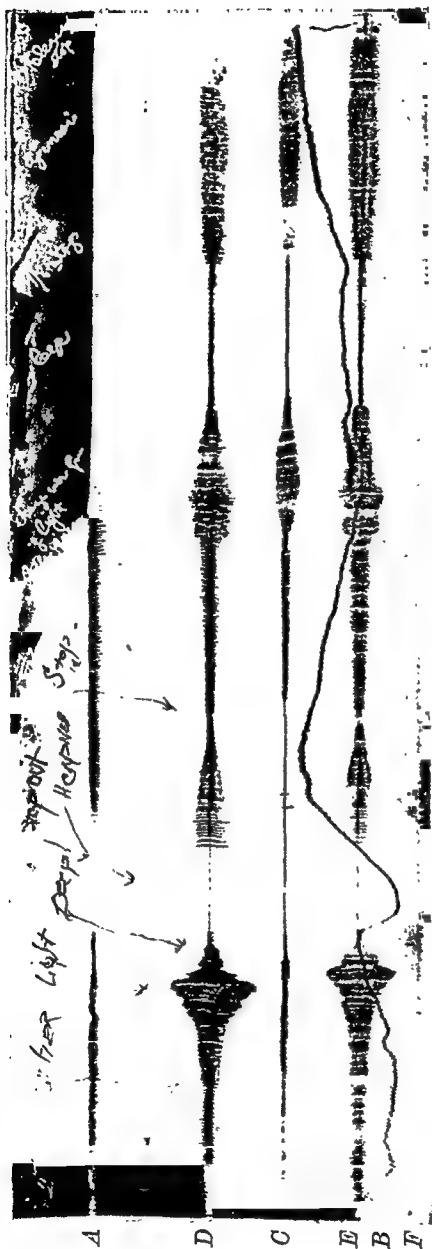


Fig. 6.—A, B, D, E, and F, are the same as in Fig. 7. C, intratracheal pressure tracing. This record shows exceedingly well the variations of the intrapleural pressure with anesthesia. Note on the left hand side of the record at second arrow the dog was light. Here the intrapleural pressure is tremendously increased, while excursions of the chest wall are diminished. A negative pressure also exists within the trachea, but is not as great as that in the intrapleural spaces. The third arrow marks the point just preceding apnea, and here the dog was under relatively deep anesthesia. The variations of blood pressure due to inspiration entirely disappear but promptly return with the resumption of active respiration. Apnea was produced by overoxygenation. Note rapid fall of blood pressure and decreased pulse pressure. Asphyxial rise, then gradual return to normal with resumption of respiration.

wall recorded as in previous experiments. Pulse rate at beginning of experiment 120. Trachea opened widely. Intrapleural pressure promptly fell to minus one to two millimeters. Blood pressure decreased. Pulse rate increased to 160. Venous pressure rose. Body temperature fifteen minutes later had dropped to 100° F., and at the end of one-half hour to 97.8° F. Color as seen in tongue was pink.

Insertion of one-eighth inch stop produced prompt increase of negative intra-

pleural pressure, rise of blood pressure, and fall of venous pressure with slowing of heart rate and respiration. In twenty minutes the body temperature was 100.8° F., and there was moderate cyanosis. Removal of the stop resulted in first a rise, and then a fall of blood pressure. Usual changes in venous pressure occurred, i.e., rise of venous pressure as blood pressure fell (Figs. 7 and 8.)

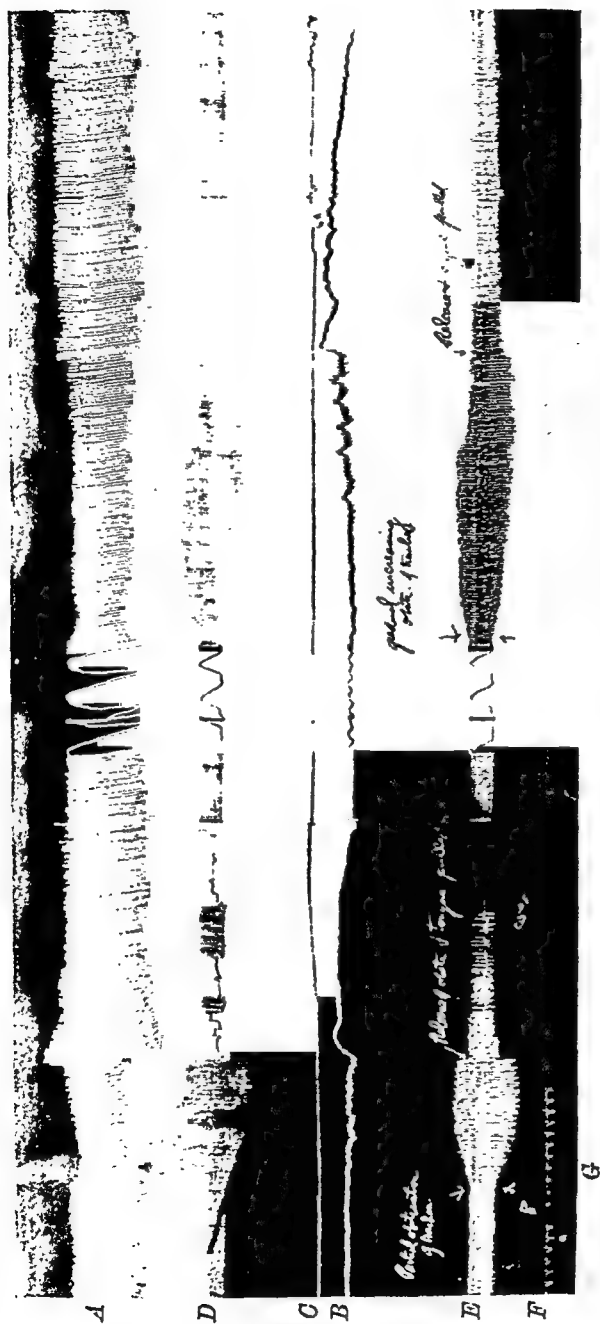


Fig. 7.—A represents excursions of chest wall; B, blood pressure tracing; C, the venous pressure changes; D and E, intrapleural pressure; F marks the time in five-second intervals. At G, the size of the air intake was reduced. Note the increased negative pressure which promptly occurred. When the intrapleural pressure was rendered less negative, note the fall in blood pressure and rise of venous pressure. This experiment shows particularly well the diminished chest excursion which occurs with obstruction and increased intrapleural pressure.

Dog given oxygen and CO_2 under slightly increased pressure, i.e., greater than atmospheric. This produced a prompt rise of venous pressure and fall of blood pressure. X-rays taken in both inspiration and expiration showed the heart to be much smaller than normal (Fig. 10). In this animal x-ray plates were also taken

at the beginning of the experiment. In corresponding phases of respiration, the positive pressure was gradually increased and after twenty minutes the dog died.

Autopsy.—Temperature at time of death was 96.7° F. The skin was cold, there



Fig. 8.—A, B, C, D, E, and F, are the same as in Fig. 7.

Note the rapid rise of blood pressure with obstruction. The fall of blood pressure with inspiration and rise with expiration are well shown, as is also the increased pulse pressure present. The individual heartbeats may be seen in the more rapid portions of the drum tracing.

Note the additional rise of blood pressure after release of the obstruction, followed by rapid fall. This we believe is due to two factors: first, the increased efficiency of ventricular contraction as the intrapleural pressure becomes less negative; and second, the increased volume of blood delivered to the ventricle as the pulmonary stasis is relieved. This is well shown by the increased chest excursions.

was practically no bleeding in cutting through the thoracic muscles preparatory to opening the thorax. The lungs were pink and relatively avascular. Heart was small and contained very little blood. On opening the abdomen there was marked dilatation of all the mesenteric vessels. Pressure in the vena cava was exceedingly high;

liver was dark red in color and when sectioned a large amount of venous blood escaped. Kidney also showed the same congestion; spleen was contracted and firm. There was no free fluid in the abdominal cavity.



Fig. 9.—A represents excursions of chest wall; B, blood pressure tracing; C represents intratracheal pressure; D and E represent intrapleural pressure; F, time intervals.

At G, note where a 1/8" stop was inserted into the negative tracheal cannula, the marked increase in intrapleural and intratracheal pressures. The excursions of the chest wall were definitely diminished, the blood pressure became elevated, and the pulse pressure markedly increased. Also note the fall of intrapleural pressures with insertion of the 1/4" stop, and the gradual fall of blood pressure and diminished pulse pressure.

The increased width of the blood pressure tracing is produced chiefly by the fall of blood pressure with inspiration. Part of this is due to actual increased filling of the heart and in some instances actual insufficiency of the aortic valve occurs. The increased CO₂ also causes relaxation of the thin-walled veins. These changes will be discussed in more detail in relation to the chemical changes in the blood.

DISCUSSION

From the consideration of the data obtained from a large number of experiments, carried out on more than 40 dogs, a definite relationship appears to exist between the intrapleural pressure and the circulation.

When there is obstruction to the inlet of air, a reduction of intrapleural pressure invariably occurs. If of a sufficient degree, a reduction of pressure also occurs within the trachea, bronchi, and alveoli. Conversely, when the size of the tracheal opening is increased, the intrapleural pressure becomes less negative, and the intratracheal pressure is so near that of the atmospheric air that it cannot be recorded by means of a mercury manometer (Fig. 9).

These changes of intrapleural pressure promptly produce alterations in the pulmonary and general circulation, causing changes in the blood pressure, venous pressure, heart rate, and body temperature. The exact mechanism by which these changes are produced cannot be entirely explained on a mechanical basis alone, as the changes of pressure within the thorax, particularly those affecting the pulmonary circulation, not



Fig. 10.—Figure on left shows x-ray appearance of heart with diminished negative intrapleural pressure. Figure on right shows dilatation of the right auricle with increased negative intrapleural pressures. Both plates were taken at the height of inspiration without changing the position of the tube.

The metal band seen in the left hand figure was not removed before taking the x-ray. This apparatus was frequently used to hold the needles in their proper position in the intrapleural spaces.

only produce mechanical effects, but these in turn involve chemical changes which react on the vital centers, and these produce reflex changes in the mechanics of the circulation. A detailed discussion of the chemistry of the blood in relation to altered peripheral resistance, respiration, etc., will be reserved for a separate communication.

Some of the important mechanical factors in relation to obstruction of the trachea and bronchi will be considered first. When there is obstruction to the inlet of air a reduction of pressure must occur in the intrapleural spaces, since the chest wall and diaphragm move away from the lung faster than the lung is able to follow them. Where the obstruction exists in the trachea above the bifurcation, the resulting re-

duction of intrapleural pressure will be approximately equal on both sides. If, however, the obstruction is in the right bronchus, then a greater reduction of pressure will occur in the right intrapleural space than on the left, although there will be some abnormal pressure on the left side as well.

This, we believe, may be explained by the fact that the mediastinum in the dog is very mobile, and the heart is displaced toward the obstructed side. This results in an abnormal stretch or pull of the opposite lung. The overstretching of the elastic tissues produces an in-

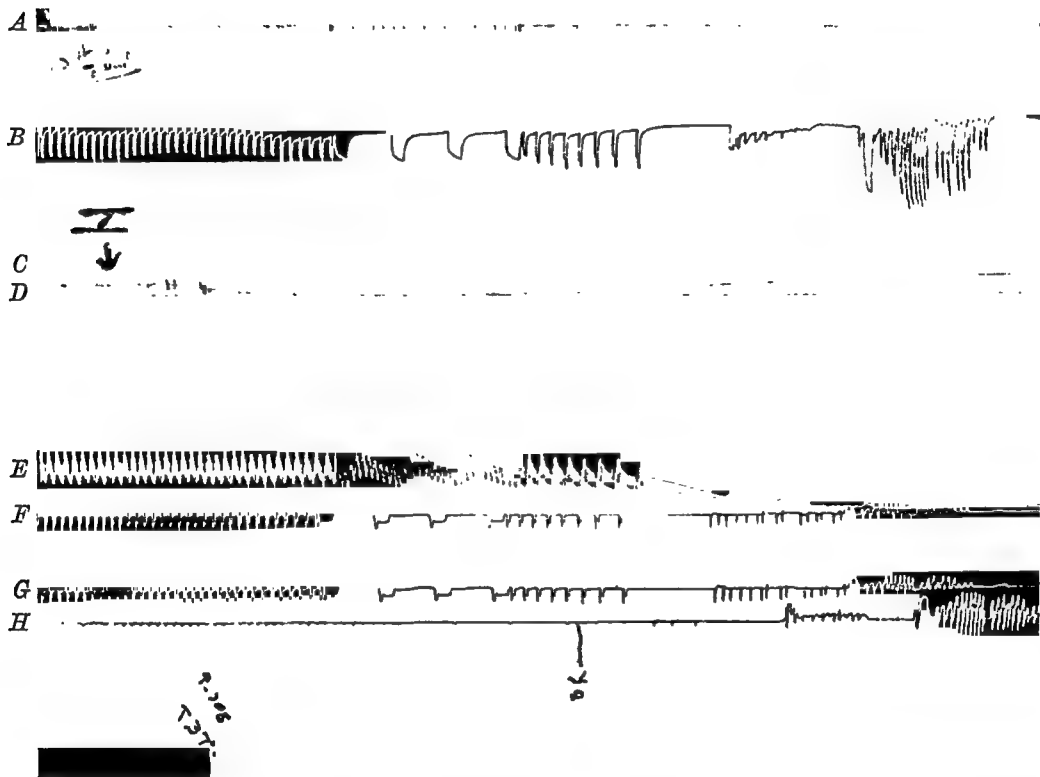


Fig. 11.—A represents time intervals; B, excursions of the chest wall; C, venous pressure tracing; D, base line for estimation of venous pressure changes; E, carotid blood pressure tracing; F, and G, intrapleural pressure readings; H, intratracheal pressure.

Note the respiratory waves in the venous pressure tracing at I. Pressure falls with inspiration and rises with expiration. With cessation of respiration these entirely disappear, although the heart is still beating. With artificial respiration they are also practically absent. Note the rise of venous pressure with cessation of respiration and gradual fall after death. This record shows particularly well the fall of blood pressure occurring with inspiration and the rise with expiration. With increasing degrees of obstruction this effect becomes even more marked. Since expiration is more forceful than normal, this also tends to produce a rise of systolic pressure.

creased separation of the lung from the chest wall. In both these instances, but more strikingly shown where the obstruction affects the trachea, there will be a diminished excursion of both the chest wall and diaphragm. This may be explained by the obstruction to inlet, the muscular effort being largely expended in reducing the pressure within the intrapleural spaces and lung itself.

This change is readily shown in the experimental record by reference to charted movements of the chest wall and diaphragm. Expiration becomes more forceful, due to the sudden release of active inspiration, in the presence of an abnormally negative intrathoracic pressure. These same pressure changes produce marked alterations in the pulmonary circulation as well as in the filling and function of the heart. Let us first consider the mechanical factors in relation to the heart itself. As the intrapleural pressure is rendered more negative a larger return of venous blood to the heart occurs, due to the reduction of pressure within the great veins of the thorax and the stretching of the heart itself during inspiration. The same reduction in pressure also increases the work of the heart not only by increasing the blood volume but also by throwing an additional load on ventricular and auricular contraction during inspiration, as the heart in this case must contract against an outside reduction of pressure tending to dilate it, in addition to the increased volume (Fig. 11). In this way, where there is sufficient obstruction of the trachea, it is relatively easy to produce an actual dilatation of the heart with insufficiency of the valves and death.

Important changes also occur in the pulmonary circulation with obstruction. Not only is there a reduction of pressure within the intrapleural spaces but also within the trachea, bronchi, and alveoli. Since the excursions of the chest wall and diaphragm are diminished with obstruction, it is obvious that the vessels coursing within the lung will not be elongated or stretched out as much as under normal conditions. Then, too, the reduction of pressure within the alveoli themselves tends to produce a dilatation or increased size of the vessels. This reduction in pressure within the alveoli will also effect the exchange of gases in the blood. As there is also some obstruction to expiration, there will be an added tendency for carbon dioxide to accumulate in the alveoli.

This increase in CO_2 will still further tend to increase the permeability of the capillaries and will contribute to the diminished flow of blood through the pulmonary circuit. The increased tortuosity and dilatation of vessels will result in a larger number of red cells flowing through the center of the vessels without actually coming in contact with the alveolar air. One must also consider that in extreme degrees of obstruction there may be a considerable reduction of available oxygen within the lung, and as a direct result of this, carbon dioxide will tend to accumulate within the alveoli and blood. Depth and rate of inspiration are increased through stimulation of the respiratory center, and the blood pressure is elevated through stimulation of the vasoconstrictor center.

The increased inflow of blood resulting from the diminished intrapleural pressure in the presence of obstruction results in an overfilling of the right auricle. A large volume of blood flows into the right ven-

tricle and with the contraction of the ventricle a considerable increase of peripheral resistance is encountered in the pulmonary circuit due to the facts previously described, i.e., diminished chest excursion, tortuosity of vessels, and dilatation of the capillaries. This results in a reflex slowing of the heart, allowing a longer recuperative or rest period.

Where the trachea is widely opened the intrapleural pressure is greatly diminished, in many instances being so nearly atmospheric that it was just recordable. In this instance the excursions of the chest wall and diaphragm are increased. The lung capillaries are well stretched out, and the velocity flow through the pulmonary circuit is increased. In this case more red cells are in contact with the capillary walls and the exchange of gases is thereby facilitated within the alveoli. There is also an adequate air supply present within the lung at approximately atmospheric pressure. The amount of blood returning to the heart is diminished, since there is less negative pressure acting on the great veins and heart. The cardiac contractions are also facilitated by the rise of pressure in the intrapleural spaces and the lung itself.

The diminished inflow, plus the squeezing action of the completely expanding lungs, results in a rise of venous pressure, fall of blood pressure, and increase of heart rate. The fall is still further aided by the increased oxygenation with relaxation of small arterioles in the periphery. As a result of the diminished venous return, the pressure in the veins within the abdomen gradually rises, and a great deal of blood may thus be lost to the general circulation by a pooling within the abdominal viscera.

This, we believe, accounts for the increased amount of blood found in the liver and kidney, and the relatively avascular conditions of the extremities in the experimental animal subjected to relatively low intrapleural pressure.

All of the above factors tend to produce a fall of body temperature, i.e., since more heat is lost through the lungs by increased pulmonary ventilation, as well as by radiation and conduction in the periphery due to the relaxation of surface vessels. This is in sharp contrast to the experiments in which the intrapleural pressure was rendered more negative, as in this instance the mechanism for normal heat loss is greatly interfered with.

The pulmonary ventilation is decidedly decreased, so that normal oxygenation and heat loss cannot occur in the lungs. Then, too, the increased carbon dioxide content of the blood produces a vasoconstriction of the peripheral vessels which seriously interferes with heat loss by radiation and conduction in the skin. In many dogs the body temperature rose to 103°-107° F. during the course of the experiment. This was most noticeable in experimental pneumonia. When the trachea

is widely opened, we have repeatedly noted a sharp fall in temperature. This occurs quite rapidly and is associated with excellent peripheral oxygenation, diminished intrapleural pressures, etc.

In general, it may be stated that variations of intrapleural pressure promptly affect the blood pressure. If the size of the tracheal inlet is decreased, the intrapleural pressure becomes more negative. Often-times the decrease is almost proportionate to the reduction of the inlet, i.e., if the size of the tracheal inlet is decreased from one-quarter inch to one-eighth inch, the intrapleural pressure is rendered almost doubly negative. This reduction of intrapleural pressure very promptly affects the filling and function of the right heart, and these volume changes, together with changes in velocity flow through the pulmonary circuit, produce prompt variations of the blood pressure, venous pressure, and pulse rate.

To be sure, reflex changes occur, affecting both the heart and the peripheral vessels, which further complicate the study; e.g., the increasing CO_2 concentration acts locally to cause relaxation of vessels within the lung and increase the permeability of the capillaries. Centrally, it acts upon the higher centers, producing increased rate and depth of respiration from stimulation of the respiratory center. The vasoconstriction center is also stimulated by the increase of CO_2 , and this produces a rise of blood pressure by increase of the peripheral resistance. It is also possible that the carotid sinus may bear some direct relation to the production of the increased blood pressure.

Where the trachea is widely opened the amount of CO_2 in the blood is diminished. There is less stimulus to the respiratory center. The intrapleural pressure rises, i.e., becomes less negative, and there is relaxation of the peripheral vessels. The rise of intrapleural pressure diminishes the inflow of blood into the heart and blood tends to collect on the venous side. The diminished effective blood volume thus soon results in a rise of pulse rate and fall of blood pressure, and the increased flow through the lungs and skin results in a fairly rapid fall of body temperature.

SUMMARY

Experiments have been carried out on the dog showing the effects of increased and decreased intrapleural pressure upon the heart, blood pressure, and pulmonic and peripheral circulation.

It has been demonstrated that rendering the intrapleural pressure more negative produces dilatation of the heart, a diminished rate of flow through the pulmonary circuit with a relative anoxemia, a slow pulse, an increased blood pressure, fall of venous pressure, and rise in body temperature.

Rendering the intrapleural pressure less negative, i.e., more nearly atmospheric, results in a fall of blood pressure, rise of venous pressure,

increased pulse rate, relatively small heart, a lowered body temperature, and an increased rate of flow through the pulmonary circuit with increased oxygenation.

An instrument has been devised for recording graphically changes in venous pressure.

The writers wish to express their appreciation to Dr. Elliott C. Cutler for his many helpful suggestions and his friendly criticism throughout the experimental work.

They also wish to acknowledge their appreciation to Eli Lilly and Company of Indianapolis, Indiana, for their generosity in establishing a grant which enabled them to carry out the initial part of the research problem.

DEFORMITY OF THE CHEST ASSOCIATED WITH EXTREME
DILATATION OF THE LEFT AURICLE. REPORT
OF TWO CASES*

EVELYN HOLT, M.D.
NEW YORK, N. Y.

SOME degree of dilatation of the left auricle is present in most patients with mitral disease, and extreme dilatation has been described in a number of cases and is now generally recognized as presenting a characteristic x-ray picture. In the more advanced stages such dilatation may cause symptoms: dysphagia from pressure on the esophagus; cough, dyspnea, hemoptysis, atelectasis or recurring attacks of bronchitis from pressure on the trachea or bronchi; or hoarseness from pressure on the recurrent laryngeal nerve. In some cases the symptoms have been so troublesome that operation has been performed—gastrotomy for a supposed carcinoma of the esophagus¹ or thyroidectomy.² Needless to say, surgical intervention failed to relieve the symptoms. Because the left auricle is situated posteriorly its enlargement, when this is sufficient to give signs, is marked by physical signs over the back—on the left, the right or on both sides—and in the right axilla. The most characteristic of these signs are dullness or dull tympany in one or both interscapular regions associated with diminished breath sounds and clearly transmitted heart sounds and murmurs and, when dilatation is extreme, a palpable systolic impulse in the right axilla. These signs may be difficult to interpret and a mistaken diagnosis of hydrothorax has led to tapping of the right chest.^{3, 4} Post-mortem examination showed that the blood which was obtained came from the left auricle, an observation that seems almost incredible until we realize that the capacity of the left auricle in such cases has been reported as 1,760 c.c.,⁵ two liters,⁶ two and one-half liters,⁷ three liters,⁸ and forty ounces after fixation.⁴

At the New York Hospital two patients have recently been under observation who have shown evidence of extreme dilatation of the left auricle and also a deformity of the chest wall, not merely a bulging of the precordial area which is seen in so many patients with large hearts or an asymmetry of the nipples as has been described by Schwartz⁹ in cases of mitral disease, but a great increase in the anteroposterior diameter of the thorax, appearing as if the sternum and the vertebral column had been pushed apart. In one case the increase in the depth of the chest was followed over a period of five years until the antero-

*From the New York Hospital and Department of Medicine, Cornell University Medical College.

posterior diameter at the level of the fourth thoracic spine actually exceeded the transverse diameter by three centimeters, and this progressive change in the shape of the chest was believed to result from the great increase in the anteroposterior diameter of the heart. As far as can be determined this particular deformity of the chest has not received special attention. In most of the reported cases of extreme dilatation of the left auricle no mention is made of the shape of the chest. Parkinson,¹⁰ however, remarked that the chest of his patient, a young man aged twenty-two years who had had dyspnea for ten years and who was found to have a remarkably dilated left auricle, was unusually deep.

REPORT OF CASES

CASE 1.—American housewife, aged thirty-seven years. This patient had chorea at seven years, occasional growing pains and frequent attacks of tonsillitis but no other illness. From the age of nineteen years she was short of breath on effort, and from the age of twenty-four years she was troubled by palpitation. When she was twenty-six years old, following unusual exertion, she had very severe and persistent dyspnea, palpitation and weakness. These symptoms persisted in spite of ten days' rest at home and led her to enter the New York Hospital (in October, 1919). At this time it was noted that she was poorly developed and nourished, dyspneic and cyanotic. The apex impulse was at the anterior axillary line; the heart rate was rapid and the rhythm totally irregular; a long rumbling diastolic murmur was heard. With rest and digitalis the patient improved and was discharged after one month. The record of this admission contains no detailed description of the shape of the chest or of the signs over the lungs.

For the next ten years the patient attended the out-patient department and took enough digitalis to control her ventricular rate. During this time she was somewhat dyspneic but was able to do clerical work for seven years, and after her marriage at thirty-three years to do her housework without undue fatigue. She never became pregnant.

In March, 1929, she was readmitted to the hospital because of nervousness and palpitation of two months' duration. The diagnosis at this time was rheumatic heart disease, mitral stenosis and insufficiency, enormous dilatation of the left auricle and auricular fibrillation. Shortly after her admission the following note was made by Dr. Conner: "Patient has the very small slender frame with poor musculature seen in so many women with mitral stenosis. Striking change in configuration of chest with increase in the anteroposterior diameter. Orthopnea, some cyanosis of lips and cheeks. Apex beat very diffuse but felt best in the sixth space in the anterior axillary line. Dullness 4.5 cm. to right and 10 cm. to left. Sharp systolic impulse followed at apex by diastolic thrill; no pulsation or thrill at base. Apical first sound very sharp and followed by a loud systolic murmur, a faint second sound and an early diastolic rumble. No distinct accentuation of P₂. In right axilla a faint but distinct systolic impulse is felt, and the two heart sounds are heard faintly. Action fairly slow and totally irregular. Over right lung in front percussion note distinctly hyperresonant as far out as anterior axillary line where dull tympany is heard, becoming *dull* in midaxilla. Behind, moderate impairment of resonance in interscapular region and below angle. Over this region vesicular murmur is very much less distinct than on left side. Exaggerated vesicular murmur in front." The liver and spleen were not palpable and there was no edema.

The x-ray films (Fig. 1) showed enormous dilatation of the left auricle, and on fluoroscopic examination the barium-filled esophagus was seen to curve backward

around the auricle. There was no delay in the passage of barium through the esophagus. Electrocardiogram showed right axis deviation and some slurring of QRS. Blood pressure was approximately 140/60 mm. Hg. Blood Wassermann reaction was negative; blood count showed slight secondary anemia. Urine showed an inconstant trace of albumin.

After a month in the hospital the patient returned to her home, remained in her usual health for six months and then died rather suddenly. The exact mode and cause of death could not be ascertained.

CASE 2.—A schoolgirl, native born of German parents, was under observation from the age of thirteen years until her death at nineteen years. At the age of four years she had a febrile attack with joint pains, called "grippe." At the age of eight years she had pertussis and at that time was said to have heart trouble. She had no other rheumatic attacks, no chorea, no tonsillitis, indeed no acute illness. When she was thirteen years old, it was noted that she had signs of mitral stenosis and an unusually large heart. A few months later the rhythm became totally irregular, and the patient was admitted to the New York Hospital (in November, 1924).

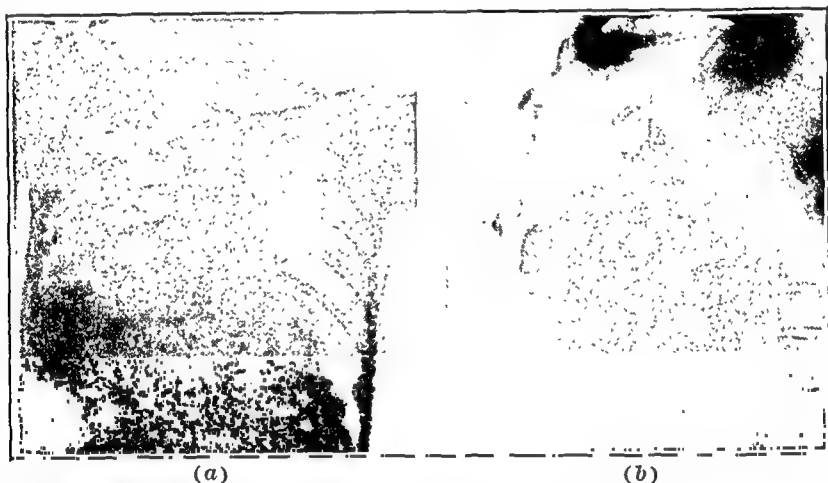


Fig. 1.—Case 1. Teleroentgenograms taken in March, 1929.

(a) Anteroposterior view showing the great cardiac enlargement with the shadow of the left auricle extending to the right of the heart almost to the chest wall.

(b) Lateral view showing the large heart filling the space between spine and sternum and the increased depth of the chest.

At this time the apex impulse was in the sixth space and the cardiac borders, as determined by percussion and by x-ray examination, extended 10 cm. to the left and 6 cm. to the right of the midline. The rhythm was irregular. The first sound at the apex was sharp and was preceded by a rumbling diastolic murmur. Electrocardiogram showed auricular fibrillation, right axis deviation and no abnormality of the ventricular waves. Quinidine restored sinus rhythm temporarily, but fibrillation promptly reappeared, and the patient was discharged on maintenance doses of digitalis. In June, 1925, she stopped taking digitalis and was readmitted to the hospital because of cardiac decompensation. The heart was slightly larger than it had been nine months earlier, but there were no new findings. After a month in the hospital the patient was sent to a convalescent home, and in November, 1925, she was admitted to the children's cardiac clinic. She attended this clinic irregularly until her death in January, 1931. A Christian Scientist, she "did not believe in taking medicine," and for weeks at a time omitted the digitalis or took less than

the dose ordered with the result that her ventricular rate was rapid much of the time. During these years she attended school and later a workshop for Class II cardiac patients; she helped with the housework and from time to time she experimented with various outside activities such as dancing and working as clerk in a shop during afternoon and evening hours. She was always short of breath on exertion and always unwilling to curtail her activities. Apart from an occasional cold or mild attack of bronchitis she had no illnesses; she had no edema of the ankles, no swelling of the liver or other evidence of congestive heart failure; she never complained of hoarseness or of dysphagia.

During the years that she was under observation there was an interesting and progressive change in the physical signs. In 1924, she was a flat-chested little girl; in 1926, she looked "round-shouldered," and it was noted that this appearance was caused by an increase in the anteroposterior diameter of the chest. This increased until it exceeded the transverse diameter. In March, 1928, the apex impulse was in the sixth space in the midaxillary line; dullness extended from the left axilla to

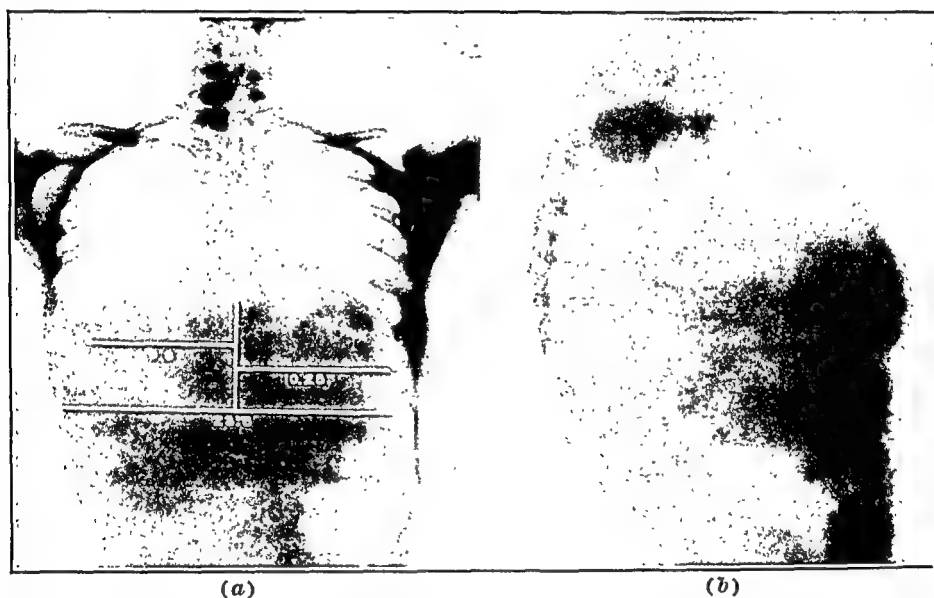


Fig. 2.—Case 2. Teleroentgenograms taken in March, 1928.

(a) Anteroposterior view showing the characteristic shape and enormous size of the heart. The haziness of the right costophrenic angle is due to the breast shadow.

(b) Lateral view showing the great increase in the distance between sternum and vertebral column.

6 cm. to the right of the midline. Over the right chest there was dull tympany anteriorly and posteriorly with dullness in the axilla, where in the fourth and fifth spaces there was a distinct systolic impulse, easily palpable and recorded on polygraphic tracing. At the apex the first sound was sharp, preceded by a diastolic rumble and followed by a systolic blow; the second sound was tapping. At the base the second pulmonic sound was accentuated. The heart sounds and murmurs were heard over the left chest posteriorly and in the right axilla. Fluoroscopic examination showed a greatly enlarged heart with the shadow of the left auricle extending backward, as seen in the first oblique position, and to the right almost to the chest wall. A year later the anteroposterior diameter of the chest, as measured with a pelvimeter, exceeded the transverse diameter; cardiac dullness extended 4 cm. to the left in the second space and reached the midaxilla in the fifth and sixth spaces; on the right it extended 6 cm. in the second space, 8 cm. in the third, 9 cm. in the

fourth and to the axilla in the fifth. There was also dullness in the third and fourth spaces in the right axilla with dull tympany in both interscapular regions and at both bases posteriorly. Over the area of dull tympany the breath sounds were diminished and the heart sounds were heard. There was little change in the patient's condition until the fall of 1930 when, owing to unusual stress at home, she became exhausted and had increased dyspnea. Late in December she caught cold and had a very troublesome cough. This cough kept her awake most of one night, and the next day she became acutely dyspneic and cyanotic and died rather suddenly. On the day of her death the heart signs were as they had been except that the rate was very rapid; bubbling râles were heard over the entire chest; there was no edema of the extremities. An autopsy was not permitted.

COMMENT

In each of these cases the most striking feature of the physical examination was the great increase in the anteroposterior diameter of the chest, and, in the absence of other factors which might explain this

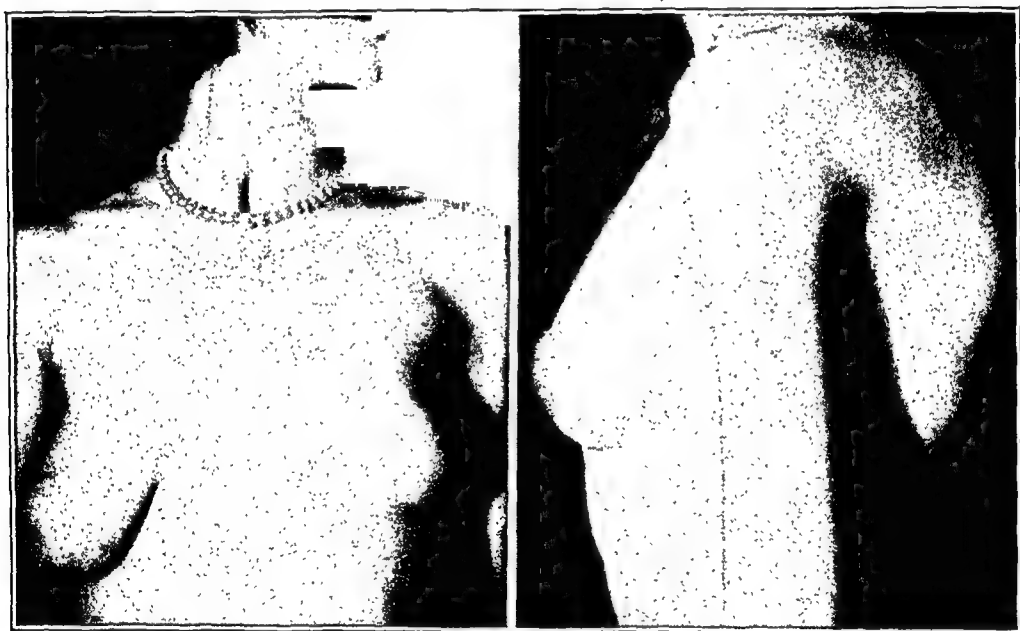


Fig. 3.—Case 2. Appearance of patient in October, 1930. Note the bulging of the precordial area, the asymmetry of the breasts, the poor muscle development and particularly the increase in the anteroposterior diameter of the chest.

deformity, it was believed that the change in the contour of the chest was secondary to the great enlargement of the heart. The change in the shape of the chest was so remarkable that for a period of about two years every child attending the children's cardiac clinic at the New York Hospital was examined for chest deformity, and in most cases measurements of the anteroposterior and transverse diameters were made and recorded. Many children showed asymmetry, bulging of the precordial area or old rachitic deformities, but no other case showing any such increase in the anteroposterior diameter as is described here was discovered. Nor was there discovered another case of extreme dilatation of the left auricle.

In reviewing the reported cases of extreme dilatation of the left auricle it would seem that the usual factors responsible for this condition are an incompetent mitral valve, disease—probably rheumatic in most cases—of the wall of the left auricle with subsequent fibrous replacement of muscle tissue, auricular fibrillation and a forceful left ventricle. Usually there is a rheumatic history but not a history of repeated rheumatic episodes with progressive cardiac damage, and in most cases the functional capacity of the patient has been remarkably good for a number of years, indicating that the left ventricle was sufficiently forceful to maintain fair compensation in spite of great mechanical disadvantages. Under these circumstances the left auricle becomes an enormously dilated sac filling the retrocardiac space and extending to the left and right. With each systole this sac transmits the force of the left ventricle, a pressure of perhaps 120 mm. Hg or more. If the conditions occur in a young person with an elastic chest, this expansile pulsation might easily force the sternum and the spine away from one another and so cause the deformity here described. This deformity may be an advantage in that the great increase in the antero-posterior diameter of the chest may explain the absence in these patients of the pressure symptoms commonly associated with extreme dilatation of the left auricle.

SUMMARY

Two additional cases of extreme dilatation of the left auricle are reported. In history, physical signs and x-ray findings these closely resemble the other cases reported in the literature.* They are remarkable, however, in that each showed a pronounced change in the configuration of the thorax. This change was believed to be secondary to the enlargement of the heart, the result of pressure exerted by the left ventricle through the dilated left auricle. It is believed that the increased depth of the chest explains the absence of those pressure symptoms which are often associated with extreme dilatation of the left auricle.

REFERENCES

1. Nichols, C. F., and Ostrum, H. W.: Unusual Dilatation of the Left Auricle, *AM. HEART J.* 8: 205, 1932.
2. Personal observation.
3. Owen, I., and Fenton, W. J.: A Case of Extreme Dilatation of the Left Auricle of the Heart, *Tr. Clin. Soc. London* 34: 183, 1901.
4. Emanuel, J. G.: Extreme Dilatation of the Left Auricle, *Lancet* 1: 591, 1923.
5. Bland, E. F., Balboni, G. M., and White, P. D.: Enormous Increase in Heart Volume With Mitral Stenosis, *J. A. M. A.* 96: 840, 1931.
6. Goedel, A.: Eine ungewöhnliche Form der Herzvergrößerung bei Mitralstenose, *Wien. klin. Wchnschr.* 42: 427, 1929.

*No attempt is made to summarize the literature on the subject of extreme dilatation of the left auricle. Reports of cases may be found in the works already cited as well as in the articles by Bramwell and Duguid¹¹, Bedford¹², Lutembacher¹³, and others, and from these papers a bibliography of the more noteworthy cases may be assembled. Other cases have been reported by men whose interest was in the pressure symptoms rather than in the heart, and doubtless many cases have been seen but not recorded in print.

7. Müller, G.: Ungewöhnliche Dilatation des Herzens und Ausfall der Verhofsfunction, *Ztschr. f. klin. Med.* 55: 520, 1905.
8. Minkowski: Demonstration eines Herzens mit ungewöhnlich starker Dilatation der Vorhöfe, *Münch. med. Wehnschr.* 51: 182, 1904.
9. Schwartz, S. P.: Displacement of the Left Nipple in Mitral Stenosis, *AM. HEART J.* 5: 344, 1929-30.
10. Parkinson, J. Porter: A Case of Unusually Great Dilatation of the Heart, *Tr. Clin. Soc. London* 34: 221, 1901.
11. Bramwell, J. C., and Duguid, J. B.: Aneurysmal Dilatation of the Left Auricle, *Quart. J. Med.* 21: 187, 1928.
12. Bedford, D. Evan: Dilatation of the Left Auricle to the Right, *AM. HEART J.* 3: 127, 1927.
13. Lutembacher, R.: Anévrysme de l'oreillette gauche, *Arch. mal. cœur.* 10: 145, 1917. Deux nouveaux cas d'anévrysme de l'oreillette gauche, *Ibid.* 11: 434, 1918. Les dilatations anévrysmales de l'oreillette gauche dans les cardiopathies mitrales, *Bull. méd.* 44: 531, 1930.

ON THE SIGNIFICANCE OF THE JUGULAR PULSE IN THE CLINICAL DIAGNOSIS OF VENTRICULAR TACHYCARDIA*

MYRON PRINZMETAL, M.D., AND FREDERICK KELLOGG, M.D.
SAN FRANCISCO, CALIF.

PAROXYSMAL ventricular tachycardia is not so rare as was formerly supposed. Since 1909, when Lewis¹ reported the first case, about seventy acceptable cases have been described. It is important to differentiate ventricular from auricular tachycardia because of the difference in prognosis and treatment. Paroxysmal auricular tachycardia is often a mild functional disorder without underlying cardiac disease. Although ventricular tachycardia may also occur in the absence of severe cardiac disease, it is usually associated with grave cardiac disease. The average duration of life in four-fifths of sixty-five cases of paroxysmal ventricular tachycardia collected by Strauss² was only twenty-four days.

ELECTROCARDIOGRAPHIC AID IN DIAGNOSIS

Most writers have considered an electrocardiogram indispensable for the diagnosis of ventricular tachycardia. The generally accepted criteria for diagnosis are outlined below:

1. The complexes must be of the ventricular form, i.e., similar to a ventricular premature beat and distinctly abnormal in form. Lewis has shown that this alone is insufficient for the diagnosis, as aberrant ventricular complexes may follow impulses arising in the auricles or junctional tissues, especially if the rate is increased.

2. Evidence of auricular activity occurring at a rate different from that of the ventricle is sufficient to make the diagnosis.

3. The onset of a paroxysm without evidence of auricular activity, preceding the first ventricular complex, is diagnostic.

4. A tachycardia of the ventricular form which occurs in the presence of long-standing auricular fibrillation is good evidence for the diagnosis.

The first criterion mentioned above must always be present and must be supplemented by one of the others. A presumptive diagnosis may be made (1) if the termination of the paroxysm is followed by a compensatory pause identical with that found after a ventricular premature beat, or (2) if ventricular premature beats of similar form to

*From the Department of Medicine, University of California Medical School, San Francisco.

ventricular complexes seen in the paroxysm have been found, or (3) if the ventricular rate varies slightly.

CLINICAL DIAGNOSIS

Strong and Levine³ and Levine⁴ pointed out that in some cases a clinical diagnosis of ventricular tachycardia can be made. They found that in ventricular tachycardia the first cardiac sound varied in intensity in definite cycles and that there was a slight irregularity in rate; in auricular tachycardia, on the other hand, the sounds were of equal intensity and occurred at regular intervals. Levine suggested that the variations might be due to auricular activity. Moreover, pressure on the vagus, carotid sinus, or eyeballs, which has been found ineffective in ventricular tachycardia, often altered auricular tachycardia. With these criteria, Levine made the correct clinical diagnosis in several cases.

In 1923, Gallavardin⁵ took a jugular pulse tracing simultaneously with an electrocardiogram in a case of paroxysmal ventricular tachycardia. He was surprised to find regular venous waves occurring at a rate less than half of the ventricular rate. These waves varied in intensity without relation to respiration. He recognized the clinical value of this observation and stated that if a jugular tracing or inspection of the jugular veins showed a recurring impulse coming at a rate about half that of the arterial rate, and if the pulsations showed variations in intensity not related to respiration, a diagnosis could be made of paroxysmal ventricular tachycardia with conservation of the normal auricular rhythm. In his later papers no further mention is made of the use of this sign clinically.

Allan⁶ and Fischer⁷ also have published tracings of the jugular pulse with simultaneous electrocardiograms in cases of ventricular tachycardia which likewise showed a slower auricular rate as manifested by the jugular pulse tracing. However, these authors failed to stress this slower jugular pulse rate as a useful clinical sign.

In view of our findings in the following case and of a review of the reported cases of proved ventricular tachycardia, it is proposed that a jugular pulse rate slower than that of the ventricles represents a sign by which a positive clinical diagnosis can be made in many cases. The mechanism of this sign is well known, but its clinical value has not been generally appreciated. It is recognized that during ventricular tachycardia the auricles may be beating independently or that retrograde rhythm may be present with or without block. If the auricular rate is slower than the ventricular rate, pulsations at this slower rate should be visible in the jugular vein. That is, the jugular pulse rate will be slower than the apical or radial rate.

Two factors serve to make the jugular pulsations prominent: first, the venous pressure is usually increased in ventricular tachycardia;

and second, since the ventricles are beating so much faster, the right auricle will frequently be contracting against a closed tricuspid valve, thus causing stasis waves in the great veins. The diagnostic value of the jugular pulse in ventricular tachycardia was noted in the following case.

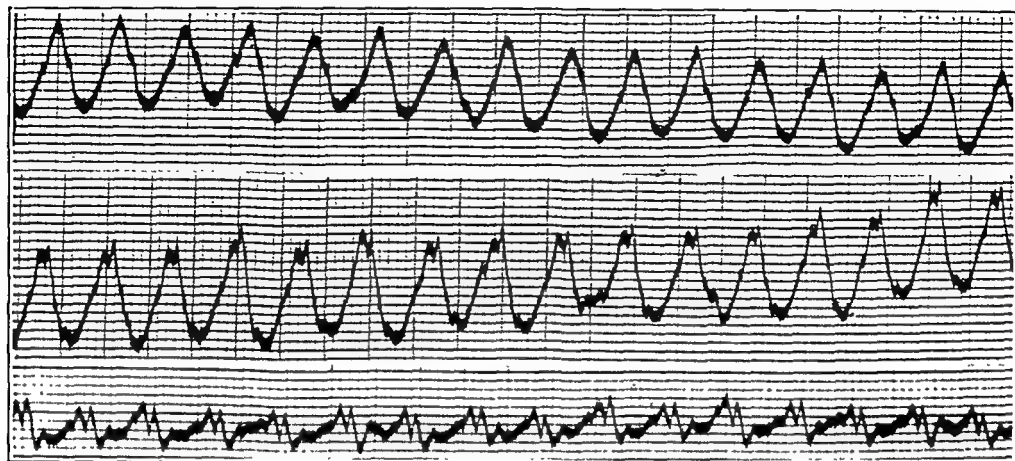


Fig. 1.—Electrocardiogram showing Leads I, II and III respectively. Definite evidence of auricular activity cannot be made out.

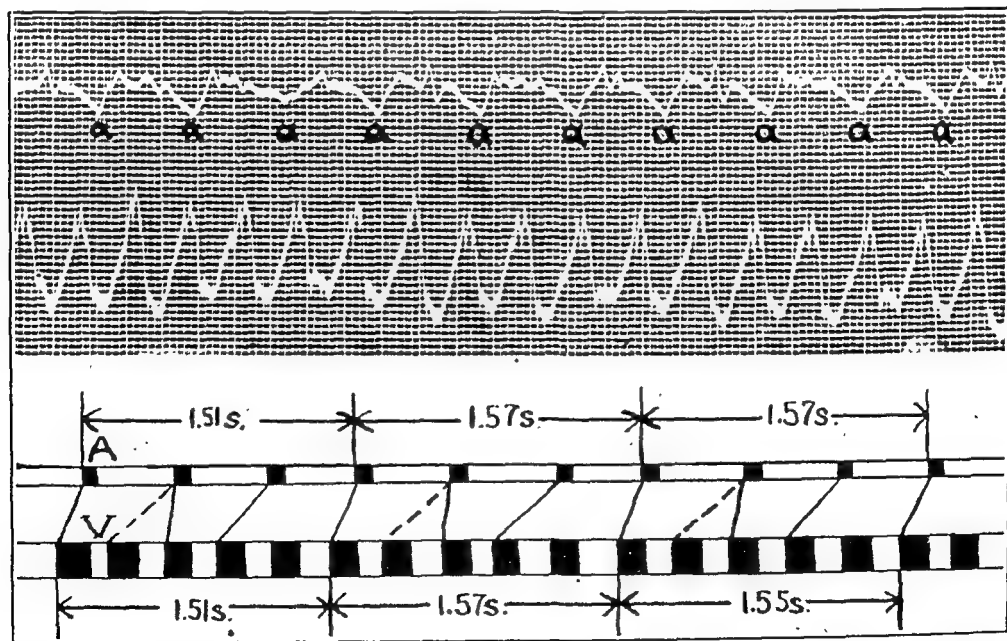


Fig. 2.—Simultaneous jugular pulse tracing and electrocardiogram (Lead II). The jugular tracing is inverted so that a-waves are negative. Auricular complexes cannot be made out definitely in the electrocardiogram.

The diagram indicates the ventriculo-auricular rhythm (retrograde conduction with 5:3 block). The auricular beats are shown in strip A, each beat corresponding with the beginning of an a-wave in the jugular tracing. The ventricular beats, corresponding with the onset of the ventricular complexes in the electrocardiogram, are shown in strip V. The solid oblique "tie" lines show unblocked impulses passing from ventricle to auricle (the dotted "tie" lines indicate alternate possibilities). The ventricular rate shows a slight irregularity. The auricular rate shows a definite irregularity which repeats itself every three beats, and the period occupied by three auricular beats corresponds, throughout, almost exactly to the period occupied by five corresponding ventricular beats.

CASE REPORT

A thirty-four-year-old male* entered the University of California Hospital with an obvious paroxysmal tachycardia which had started four hours before. He had enjoyed comparatively good health except for numerous similar attacks in the previous four years. On examination, the patient was seen to be cyanotic and orthopneic. His heart was slightly enlarged to the left and was beating with an apical rate of

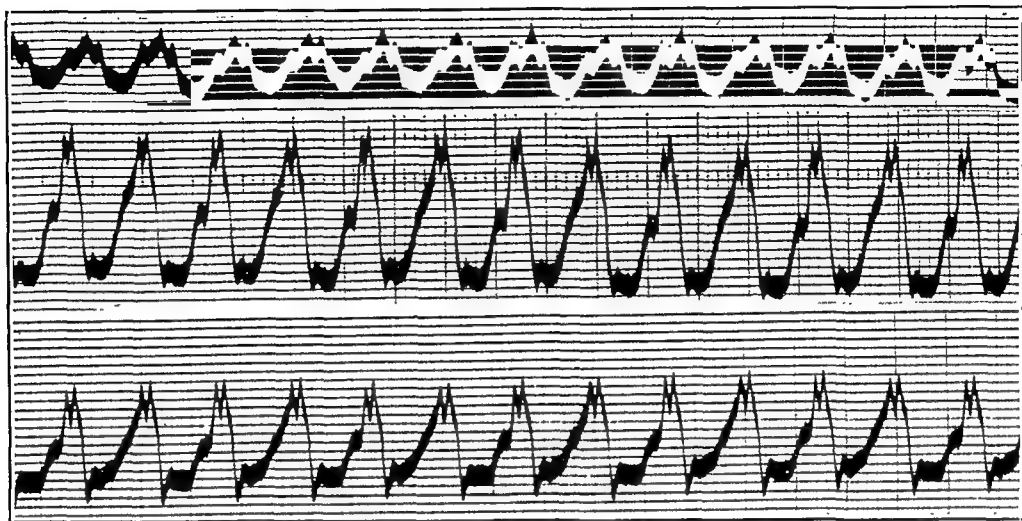


Fig. 3.—Electrocardiogram showing Leads I, II and III taken at another time. Evidence of auricular activity occurring on alternate ventricular complexes is clearly shown in Leads II (probable retrograde conduction with 2:1 block).

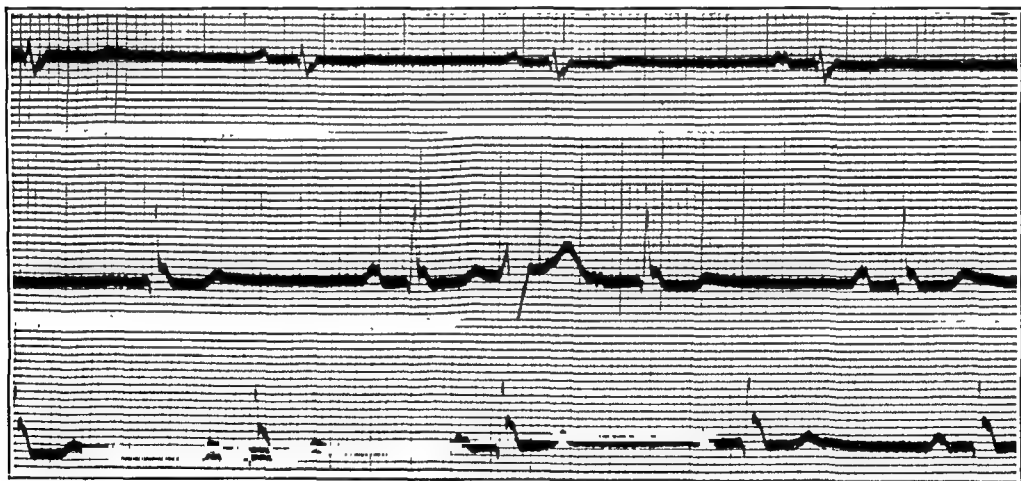


Fig. 4.—Electrocardiogram showing Leads I, II and III respectively after the tachycardia.

about 195 per minute. No irregularity in time or intensity of the first sound was detected. The jugular bulb and vein were pulsating distinctly at a rate of 115 per minute. The pulsations were obviously stasis waves and the veins were full even in the upright position. Since the ventricles were beating more rapidly, these waves were assumed to be due to auricular activity at a slower rate. This could not occur in auricular tachycardia, and therefore a diagnosis of ventricular tachycardia

*This patient was Case 1 in the report by Sampson and Anderson⁵ on the treatment of cardiac arrhythmias with potassium salts.

was made. The electrocardiogram (Fig. 1), which showed a slight irregularity in rate, did not show evidence of auricular activity (P-waves) at this time, and therefore a positive diagnosis by this means was not possible. The jugular pulse tracing (Fig. 2) showed definite a-waves occurring with an irregularity which repeated itself every three beats. The period occupied by each three auricular beats was of the same length as the period occupied by five ventricular beats. In other words, as shown by the diagram, a retrograde rhythm with a net 5:3 block was present. At this time, therefore, the jugular pulsations were necessary to make a definite diagnosis of ventricular tachycardia, which would have been impossible to make from the electrocardiogram alone. At another time an electrocardiogram (Fig. 3) of this patient did show evidence of auricular activity at a rate slower than the ventricular rate (probable retrograde rhythm with 2:1 block). Fig. 4 shows the electrocardiogram of this patient following the tachycardia.

LIMITATIONS OF THE SIGN

This sign, the slower jugular pulse, has definite limitations which, fortunately, can be determined at the present time by a review of the reported cases. The sign is valueless in cases with coexisting auricular fibrillation; in cases in which the auricles are beating as rapidly as the ventricles (only one such proved case on record, [Scott]); and in the rare case of nodal tachycardia* in which this sign might also be present. The sign would be valuable, however, in many instances (as in the case reported) when the electrocardiogram fails to show evidence of slower auricular activity, and when, as is usually the case, the onset of the paroxysm is not recorded. In these cases a clinical diagnosis might be made which would be impossible to make from the electrocardiogram alone. If, as Levine suggests, irregularities in the first cardiac sound are due to auricular activity, the same limitations would apply to his sign.

ANALYSIS OF CASES

Including our own, we have analyzed sixty-eight reported cases of proved paroxysmal ventricular tachycardia, which are tabulated in Table I with respect to the state of the auricles. A number of cases, many of which might have been paroxysmal auricular tachycardia with aberration of the ventricular complexes, were rejected as not fulfilling the criteria outlined above.

Of the sixty-eight cases there were ten diagnosed by recording the onset of the paroxysm, in which the state of the auricles could not be determined. Of the remaining fifty-eight, auricular fibrillation, or occasionally flutter, was present in twenty-one. Of the remaining thirty-seven, there was only one case of ventricular tachycardia with a retrograde 1:1 rhythm. An independent auricular rhythm was present in twenty-five cases, and eight cases showed retrograde rhythm with partial block. Three cases showed auricular complexes occurring more slowly

*So far as known, ventricular tachycardia cannot be distinguished from nodal tachycardia with aberration of the ventricular complexes.

TABLE I

	RHYTHM OF AURICLES					
	FIBRILLATION OR FLUTTER	RETROGRADE 1:1 RHYTHM	RETROGRADE RHYTHM WITH PARTIAL BLOCK	INDEPENDENT RHYTHM	AURICULAR RHYTHM UNKNOWN THOUGH P- WAVES ARE SEEN	NO P-WAVES MADE OUT
Allan, Geo. A.: Glasgow M. J. 107: 74, 1927.			1			
Anderson, M. C.: Am. J. M. Sc. 181: 369, 1931.				1		
Barrier, C. W.: J. A. M. A. 89: 742 1927.				1		
Butterfield, H. G., and Hunt, G. H.: Quart. J. Med. 7: 209, 1914.				1		
Clarke, R. Manning: Calif. & West. Med. 32: 252, 1930.					1	
Cohn, Alfred E.: Am. J. M. Sc. 151: Eakin, W. W.: Canad. M. A. J. 51: 1454, 1926.				1		
1926.					1	1
Felberbaum, David: Am. J. M. Sc. 166: 211, 1923.						1
Fischer, Robert: Wien. Arch. f. inn Med. 14: 405, 1927.				1		
Gallavardin, Louis: Arch. des mal du coeur 13: 121, 1920.				1		
Ibid.: 13: 207, 1920.	1					
Ibid.: 13: 210, 1920.	1					
Ibid.: 15: 298, 1922.				1		
Ibid.: 19: 153, 1926.	2					1
Gilchrist, A. R.: AM. HEART J. 1: 546, 1925-26.	1			2		1
Hart, S. T.: Heart 4: 128, 1912-13.			1			
Hollingsworth, E. W.: Ann. Int. Med. 5: 1506, 1931-32.				1		
Jones, T. D., and White, P. D.: AM. HEART J. 2: 139, 1926-27.				1		
Kerr, W. J., and Bender, W. L.: Heart 9: 269, 1921.	1					
Levine, S. A., and Curtis, A. N.: AM. HEART J. 1: 413, 1925-26.	1					
Levine, S. A.: AM. HEART J. 3: 177, 1927-28.						1
Levine, S. A., and Fulton, M. N.: J. A. M. A. 92: 1162, 1929.	1			2		
Levy, R. L.: Arch. Int. Med. 30: 451, 1922.	2					
Lewis, Thomas: Lancet 1: 382, 1909.				1		
Lewis, Thomas: Mechanism of the Heart Beat, London, 1911, p. 168.				1		
Luten, Drew: Arch. Int. Med. 35: 74, 1925.				1		
Ibid.: 35: 74, 1925.	2					
Marvin, H. M.: Heart 10: 279, 1923			1			
Marvin, H. M.: AM. HEART J. 4: 21, 1928-29.	1			2	1	

TABLE I—CONT'D

	RHYTHM OF AURICLES					
	FIBRILLATION OR FLUTTER	RETROGRADE 1:1 RHYTHM	RETROGRADE RHYTHM WITH PARTIAL BLOCK	INDEPENDENT RHYTHM	AURICULAR RHYTHM UNKNOWN THOUGH P- WAVES ARE SEEN	NO P-WAVES MADE OUT
Marvin, H. M., and White, P. D.: Arch. Int. Med. 29: 403, 1922.			1			
McMillan, T. M., and Bellet, S.: AM. HEART J. 7: 70, 1931-32.				1		
Moore, H.: Irish J. M. Sc. 36: 754, 1928.			1			
Orsi, A., and Villa, L.: Arch. d. mal du coeur 21: 353, 1928.	1					
Porter, Wm. B.: J. Am. M. Sc. 167: 821, 1924.				1		
Reid, W. D.: Arch. Int. Med. 33: 23, 1924.				1		
Ritchie, W. T.: Edin. M. J. 33: 193, 1926.						1
Robinson, G. C., and Herrman, G. R.: Heart 8: 59, 1921.			2	1		
Schwenson, C.: Heart 9: 199, 1921-22.	1					
Scott, R. W.: Heart 9: 297, 1921.		1				
Singer, R., and Winterberg, H.: Wien. Arch. f. inn. Med. 3: 329, 1922.						1
Strauss, M. B.: Am. J. M. Sc. 179: 337, 1930.	2					
Strong, G. F., and Levine, S. A.: Heart 10: 125, 1923.						1
Vaughan, W. T.: Arch. Int. Med. 21: 381, 1918.						1
White, P. D., and Palmer, R. S.: AM. HEART J. 3: 454, 1927-28.	1			1		
Willius, F. A.: Bost. M. & S. J. 178: 40, 1918.						1
Willius, F. A.: Ann. Clin. Med. 3: 537, 1925.				1		
Wolferth, C. C., and McMillan, T. M.: Arch. Int. Med. 31: 184, 1923.	3		1	1		
Present case report.						
Total	21	1	8	25	3	10

Cases in which sign would be absent..... 22

Cases in which sign should be present..... 36

Cases in which status of sign is not known..... 10

than the ventricular complexes, though the exact auricular rhythm could not be determined. Thus in thirty-six out of the fifty-eight cases in which it was possible to determine the auricular rhythm, it should have been possible to diagnose ventricular tachycardia by the jugular pulse.

If the onset of the paroxysm had not been recorded, an accurate electrocardiographic interpretation would have been impossible in ten of

the reported cases. Moreover, in our case, it was not possible to make a positive diagnosis from the first electrocardiogram. Consequently, there are probably a number of cases of ventricular tachycardia which cannot be differentiated electrocardiographically from auricular tachycardia with aberration of the ventricular complexes.

The presence of jugular pulsations occurring more slowly than the apical rate would be a valuable aid in the diagnosis of such cases. However, a jugular pulse at the same rate as the apical rate would not rule out ventricular tachycardia, as a 1:1 retrograde rhythm might be present.

SUMMARY AND CONCLUSIONS

1. Paroxysmal ventricular tachycardia may often be differentiated clinically from auricular tachycardia when jugular pulsations at a slower rate than the apical rate are present.

2. A case is reported in which a diagnosis of paroxysmal ventricular tachycardia could not be definitely made from the electrocardiogram, but in which the diagnosis was made by the presence of jugular pulsations. It is suggested that there may be many similar cases in which this clinical sign alone could make a positive diagnosis, or in which it would be a necessary supplement to the electrocardiogram in diagnosis.

3. During ventricular tachycardia the most common auricular rhythms in the order of frequency are: an independent rhythm, auricular fibrillation, and retrograde rhythm with partial block.

4. The sign discussed in this paper has limitations but is applicable to about two-thirds of the reported cases. The coexistence of auricular fibrillation is the only important condition which renders the sign valueless.

REFERENCES

1. Lewis, Thomas: Single and Successive Extrasystoles, *Lancet* 1: 382, 1909.
2. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.* 179: 337, 1930.
3. Strong, G. F., and Levine, S. A.: The Irregularity of the Ventricular Rate in Paroxysmal Ventricular Tachycardia, *Heart* 10: 125, 1923.
4. Levine, S. A.: Clinical Recognition of Paroxysmal Ventricular Tachycardia, *AM. HEART J.* 3: 177, 1927.
5. Gallavardin, L.: Tachycardie paroxystique ventriculaire, *Arch. des mal. du coeur* 13: 121, 1920.
6. Allan, G. A.: Tachycardia, *Glasgow M. J.* 107: 74, 1927.
7. Fischer, Robert: Ueber unregelmässige ventrikuläre Tachykardie, *Wien. Arch. f. inn. Med.* 14: 405, 1927.
8. Sampson, J. J., and Anderson, E. M.: The Treatment of Certain Cardiac Arrhythmias With Potassium Salts, *J. A. M. A.* 99: 2257, 1932.

THE CREATINE CONTENT OF THE MYOCARDIUM OF NORMAL AND ABNORMAL HUMAN HEARTS*

DONALD W. COWAN, M.D.
IOWA CITY, IOWA

IT IS the general belief today that the immediate energy for the contractile process of skeletal muscle is derived from the breakdown of phosphocreatine.¹ This view has been extended recently by Clark, Eggleton and Eggleton² to include the contraction of cardiac muscle.

Because of the rapid breakdown of phosphocreatine after the death of a tissue, it is very difficult to study the concentration of this substance in human muscle. Creatine alone, however, is relatively stable and therefore can be estimated with little difficulty.

Skeletal muscle shows a decrease in creatine content in several pathological conditions accompanied by muscular weakness.³⁻⁹ As Myers, in his recent review,¹⁰ stated: "The potential muscular efficiency appears to depend upon the creatine content of the muscle. . . ."

The work herein presented was carried out to test whether this generalization would hold true in the case of the myocardium. Relatively few reports are available concerning the creatine content of the human heart, and these apparently deal only with the normal.

MATERIALS AND METHODS

Portions of left ventricular myocardium were obtained from 80 cases coming to autopsy at the University of Iowa Hospitals. These cases, although not consecutive, were not selected; the diagnosis in each case was unknown to me until after the analyses were completed and the results computed. Approximately the same part of the ventricle was used in each case in order to avoid possible errors due to differences in creatine content of the various parts of the musculature.

The following method of preparing the samples was adopted: The fresh piece of tissue was placed upon a piece of filter paper, and a rectangular block was cut from it entirely devoid of epicardium, endocardium, and papillary muscle. After this block had been blotted free of blood and moisture, its two ends were sliced off and discarded. Then it was divided into three approximately equal portions each of which had thus been dried to an equal degree. These portions were immediately placed in weighing bottles and weighed. Two were used for duplicate creatine analysis; the third was dried in an electric oven at 100° C. to constant weight.

Obviously this method of determining the water content may not allow accurate comparison of the water-solid ratio of two different hearts prepared separately; however, it does indicate accurately the water content of the pieces from the same block which were used for creatine determinations. Thus the creatine contents can be listed in comparable values.

*From the Department of Physiology, State University of Iowa, College of Medicine.

Creatine was measured as creatinine according to the method of Rose, Helmer and Chanutin,¹¹ and is reported in terms of creatine. There was an average difference of slightly more than 3 per cent between duplicates.

RESULTS

Of the 80 hearts used in this investigation, 48 are classified here as normal, 17 as decompensated hearts, and the remaining 15 fall into a miscellaneous group.

Normal Hearts

Included in this group are the hearts from patients with proved diagnoses of pneumonia, empyema, lung abscess, bronchiectasis, tuberculosis, carcinoma of the bronchus, pulmonary embolism, otitis media, mastoiditis, lateral sinus thrombosis, cerebral hemorrhage, skull fracture, brain tumor, meningitis, encephalitis, neurosyphilis, septicemia, carcinoma of various parts of the digestive tract, duodenal ulcer, intestinal obstruction, strangulated hernia, peritonitis, cholecystitis, toxic necrosis of the liver, pancreatitis, uremia, urinary tract infection, nephritis, carcinoma of the bladder, carcinoma of the cervix, carcinoma of the breast, carcinomatosis, actinomycosis, cellulitis, pemphigus, osteomyelitis, extensive burns, severe hemorrhage, pernicious anemia, diabetes, Hodgkin's disease, lymphoblastic lymphoma, and amyotrophic lateral sclerosis.

Strictly speaking, the hearts from many of these cases could not be called perfectly normal from an anatomical point of view. In fact, if all hearts showing slight cloudy swelling, slight brown atrophy, or sclerosis of the proximal coronary arteries were excluded from this normal group, only a few would remain. As it is, all hearts which gave no clinical symptoms, as far as could be ascertained from the records, were included in this group unless they presented rather marked gross or microscopic anatomical changes. The results of the analyses of the 48 normal hearts are summarized in Table I.

TABLE I
FORTY-EIGHT NORMAL HEARTS

	MEAN	STANDARD DEVIATION
Creatine, mg. per cent of moist weight	202	37
Water, per cent	79.17	1.04
Creatine, mg. per cent of dry weight	971	165
Comparable creatine,* mg. per cent	194	33

*The comparable creatine value is the creatine content of moist tissue based upon an arbitrary standard water content of 80 per cent. It is obtained by dividing the dry weight value by 5.

The standard deviation for the comparable creatine in this table indicates very good agreement among the individual samples. There were a few cases in this group, however, in which there was considerable

deviation from the mean. These cases are listed here in detail. Perhaps further work will indicate why they are so different from the rest in regard to creatine content.

SAMPLE NO.	DIAGNOSIS	COMPARABLE CREATINE, MG. PER CENT
7	Prostatic hyperplasia. Chronic bilateral ureteritis and pyelonephritis. Acute gangrenous cystitis. Acute uremia. Bronchopneumonia. Streptococcus septicemia.	117
63	Carcinomatosis: Breast, regional nodes, mediastinum, liver, retroperitoneal nodes, adrenals.	117
51	Malignant lymphoma, lymphoblastic type. Lateral sinus thrombosis. Septicemia. Secondary anemia. BMR = +20.9%. Heart: Some coronary sclerosis and brown atrophy.	134

Influence of Sex.—That there is no difference in creatine content of the heart of the two sexes is shown in Table II.

TABLE II
INFLUENCE OF SEX ON THE CREATINE CONTENT OF THE NORMAL HEART

SEX	NUMBER OF CASES	COMPARABLE CREATINE MG. PER CENT
Male	30	193
Female	18	196
Total	48	194

SAMPLE NO.	DIAGNOSIS	COMPARABLE CREATINE, MG. PER CENT
3	Cellulitis, right arm. Streptococcus septicemia. General sepsis. Bronchopneumonia. Arteriosclerosis. Heart: Some coronary sclerosis and brown atrophy.	144
39	Carcinoma of the transverse and sigmoid colon. Intestinal obstruction. Fecal fistula. Thrombophlebitis, right iliac vein. Pulmonary emboli. Septicemia. Heart: Some brown atrophy.	244
40	Malignant lymphoma, Hodgkin's type. Bronchopneumonia. Arteriosclerosis.	244
18	Carcinoma of the cervix. Gangrene of the pelvic organs. Hydronephrosis and hydroureter. Uremia. Generalized arteriosclerosis. Heart: Some brown atrophy.	251
17	Acute and chronic cholecystitis with stones. Cholecystoduodenal fistula, perforation of gallbladder. Acute intestinal obstruction. Acute gangrenous ileitis, generalized peritonitis. Diabetes mellitus. Generalized arteriosclerosis. Heart: Some brown atrophy and cloudy swelling.	262

Influence of Age.—The ages of the individuals in the normal group ranged from five months to sixty-nine years. Contrary to the findings in skeletal muscle, in which young individuals have lower creatine con-

tents, there is no apparent difference in cardiac creatine at different ages (Table III).

TABLE III

INFLUENCE OF AGE ON THE CREATINE CONTENT OF THE NORMAL HEART

AGE	NUMBER OF CASES	COMPARABLE CREATINE MG. PER CENT
Under 1 year	1	203
1-9 inclusive	4	194
10-19 inclusive	none	
20-29 inclusive	6	177
30-39 inclusive	9	195
40-49 inclusive	6	195
50-59 inclusive	11	204
60-69 inclusive	11	192
Total	48	194

Decompensated Hearts

There were 17 cases that showed evidence of cardiac decompensation either clinically or at post-mortem examination. Some of these were frank insufficiencies, obviously the cause of death, while other cases were only mildly decompensated. This group is made up mostly of hypertensive hearts, rheumatic valvular hearts and nephritic hearts. There was one case of pernicious anemia with brown atrophy and resulting heart failure. There was one case of chronic adhesive pericarditis with failure. Table IV is a summary of the results found in this group.

TABLE IV

SEVENTEEN DECOMPENSATED HEARTS

	MEAN	STANDARD DEVIATION
Creatine, mg. per cent of moist weight	147	37
Water, per cent	79.47	0.87
Creatine, mg. per cent of dry weight	720	185
Comparable creatine, mg. per cent	144	37

In comparing these results with those found in the normal cases, it is seen that the creatine content of the decompensated hearts averages 50 mg. (25.8 per cent) lower than the normal. Statistically it is found that, according to Fisher's formula,¹² "t" is equal to 5.1. This indicates that the difference between the normal group and the decompensated group is highly significant.

It might be pointed out that of these 17 decompensated hearts, 6 fell within the normal range. The remaining 11, however, were definitely low, their values ranging from 92 to 152 mg. of creatine per 100 grams of tissue.

The question naturally arises whether the lower creatine content of the decompensated heart is due to an actual decrease in the creatine of the muscle fiber itself, or to other changes which might alter the relative

amount of muscular tissue in the myocardium. It is known that fibrous tissue contains much less creatine than muscular tissue. Scarring, therefore, lowers the creatine content of a muscular organ. Although great care was taken to avoid using portions which contained gross scar tissue, it is obviously impossible to exclude the microscopic "patchy areas of scarring" in hearts which contain it.

That the factor of increased fibrous tissue is negligible in this series, however, is shown by the fact that the hearts with scarring had a higher average creatine content (153 mg.) than those in which no increase of fibrous tissue was reported (136 mg.).

It is interesting to note that some of the lowest creatine values were obtained in decompensated hearts which, aside from hypertrophy, were without any obvious pathological change, either macroscopic or microscopic.

Miscellaneous Group

Fifteen cases are listed here which were not decompensated, but which could not be included in the normal series. They include cases with clinical manifestations of cardiac disease, pathological evidence of myocardial damage, hypertrophied hearts (compensated), etc.

SAMPLE NO.	DIAGNOSIS	COMPARABLE
		CREATINE, MG. PER CENT
31	Gas gangrene following perforating gunshot wound of chest. Profound shock. Sepsis. Myocardium shows extensive degenerative changes.	68
11	Tb. Nephritis. Auricular fibrillation.	144
32	Ruptured aortic aneurysm resulting in hemopericardium. Cardiac hypertrophy.	152
65	Diabetes. Chronic vascular nephritis. Terminal uremia. Hypertension. Cardiac hypertrophy. Acute streptococic pericarditis. Some scarring of myocardium, some coronary sclerosis.	158
28	Renal carcinoma extending into renal vein, vena cava, and right auricle. Cause of death, neoplastic pulmonary embolus. Heart hypertrophied and dilated.	159
14	Osteomyelitis. Septicemia. Urinary infection with retention. Myocardium shows cloudy swelling, fragmentation, vacuolization.	159
34	Adenocarcinoma of sigmoid colon. Postoperative peritonitis. Septicemia. Adiposity of heart. (Muscle fibers separated by numerous strands of fat cells which extend nearly through the entire width of the myocardium.)	163
29	Empyema. Auricular fibrillation.	164
30	Old rheumatic valvular heart disease (compensated) with auricular fibrillation, cardiac hypertrophy and dilatation. Acute endocarditis. Septicemia. Septic emboli to vessels and spleen.	165
79	Chronic vascular nephritis with terminal uremia. Arteriosclerosis. Hypertension. Cardiac hypertrophy. Fibrinous pericarditis. Coronary sclerosis.	172

42	Bronchopneumonia following fracture of femur. Septicemia. Thrombophlebitis. Acute vegetative endocarditis. Slight cardiac enlargement.	173
35	Adenoma of thyroid. Septicemia. Thrombophlebitis. Infarcts of kidneys and spleen. Left cardiac enlargement. Auricular fibrillation. Hypertension.	174
60	Carcinoma of larynx, with laryngeal obstruction. Arteriosclerosis. Hypertrophy and dilatation of the heart. Some scarring of the myocardium.	189
41	Otitis media and mastoiditis with overwhelming septicemia; involvement of brain, kidneys, vessels, spleen, meninges, heart. Acute bacterial endocarditis, acute myocarditis, acute pericarditis.	195
72	Chronic vascular nephritis. Hypertension. Cardiac hypertrophy and dilatation. Acute parotitis. Acute pneumonia. Some myocardial scarring.	208

TABLE V
FIFTEEN MISCELLANEOUS HEARTS

	MEAN	STANDARD DEVIATION
Creatine, mg. per cent of moist weight	165	30
Water, per cent	79.68	0.65
Creatine, mg. per cent of dry weight	814	151
Comparable creatine, mg. per cent	163	30

Table V summarizes the results of the miscellaneous group.

It is evident that the creatine content of this group falls between the value found for the normals and that found for the decompensated hearts. This is shown graphically in Chart 1. That this group has a creatine value which is definitely lower than normal is shown by the fact that Fisher's "t" is equal to 3.1.

EFFECT OF SEPTICEMIA ON CREATINE CONTENT OF THE HEART

Denis⁶ reported that septicemia is accompanied by a loss of creatine from the skeletal muscles. That such is apparently not the case in cardiac muscle is shown in Table VI.

TABLE VI
EFFECT OF SEPTICEMIA ON THE CREATINE CONTENT OF THE HEART

	SEPTICEMIA PRESENT		SEPTICEMIA ABSENT	
	NUMBER OF CASES	COMPARABLE CREATINE, MG. PER CENT	NUMBER OF CASES	COMPARABLE CREATINE, MG. PER CENT
Normal group	34	193	14	197
Decompensated group	9	145	8	143
Miscellaneous group	9	164	6	161

EFFECT OF HYPERTROPHY PER SE ON THE CREATINE CONTENT

In the decompensated series, all but three hearts were hypertrophied. These three averaged 149 mg. of comparable creatine per 100 grams of tissue, which is not significantly different from the average for this series.

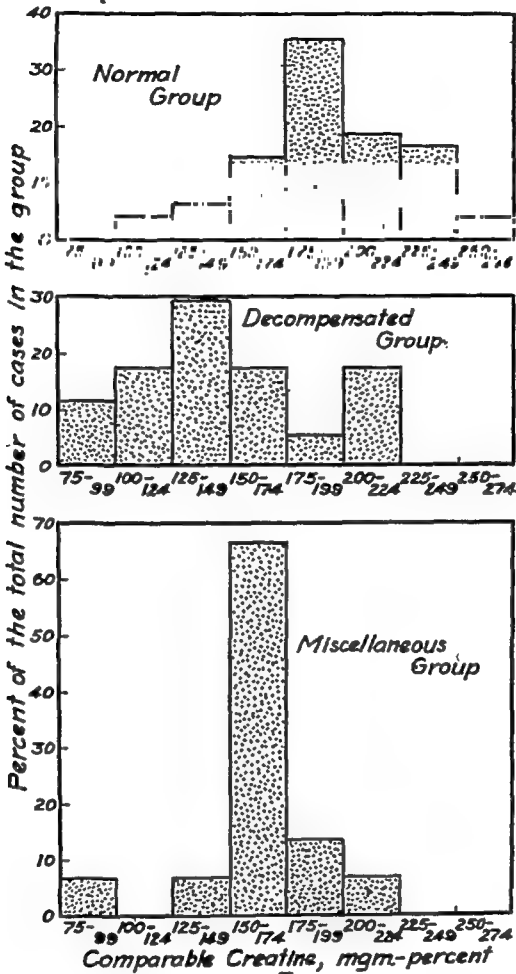


Chart 1.—Comparison of comparable creatine content of normal, decompensated, and miscellaneous hearts.

In the miscellaneous series the results are as listed in Table VII. The difference between the means in this comparison is 23. The value of “t” in Fisher’s formula is 1.5, which is too low to show much significance; it indicates that there is a possibility that the hypertrophied hearts have a higher creatine content as compared with nonhypertrophied hearts.

TABLE VII
EFFECT OF HYPERTROPHY ON THE CREATINE CONTENT OF THE HEART
(MISCELLANEOUS GROUP)

	NUMBER OF CASES	COMPARABLE CREATINE, MG. PER CENT
Hypertrophied	9	172
Not hypertrophied	6	149

SUMMARY

The left ventricular myocardium of 48 approximately normal human hearts had an average creatine content of 194 mg. per 100 grams of tissue, this value being based upon an arbitrary water content of 80 per cent.

There were neither sex nor age differences in this creatine content.

A few cases included in the normal group, but having creatine contents differing widely from the mean, are listed separately with diagnoses given in detail.

Analyses of 17 decompensated hearts showed a significantly lower average creatine content than normal. Scar tissue was not a significant factor in producing this low value.

Fifteen abnormal, but not decompensated, hearts had an average creatine content significantly lower than normal, but higher than the values for the decompensated hearts. These are listed separately, with their diagnoses given in detail.

Septicemia per se had no effect upon the creatine content of the left ventricle.

An effect of hypertrophy per se on the creatine content of the heart was not definitely established.

These findings suggest that the "reserve" of the heart closely parallels its creatine content.

I am indebted to the Staff of the Pathology Department for making the post-mortem material and the records available.

REFERENCES

1. Hill, A. V.: Revolution in Muscle Physiology, *Physiol. Rev.* 12: 56, 1932.
2. Clark, A. J., Eggleton, M. G., and Eggleton, P.: Phosphagen in the Perfused Heart of the Frog, *J. Physiol.* 75: 332, 1932.
3. Chisholm, R. A.: The Creatine Content of Muscle in Malignant Disease and Other Pathological Conditions, *Biochem. J.* 6: 243, 1911-12.
4. Myers, V. C., and Fine, M. S.: The Influence of Starvation Upon the Creatine Content of Muscle, *J. Biol. Chem.* 15: 283, 1913.
5. Shaffer, P. A.: Observations on Creatine and Creatinine, *J. Biol. Chem.* 18: 525, 1914.
6. Denis, W.: Creatine in Human Muscle, *J. Biol. Chem.* 26: 379, 1916.
7. Williams, B. W., and Dyke, S. C.: Observations on Creatinuria and Glycosuria in Myasthenia Gravis, *Quart. J. Med.* 15: 269, 1922.
8. Bodansky, M., Schwab, E. H., and Brindley, P.: Creatine Metabolism in a Case of Generalized Myositis Fibrosa, *J. Biol. Chem.* 85: 307, 1929.
9. Goettsch, M., and Brown, E. F.: Muscle Creatine in Nutritional Muscular Dystrophy of the Rabbit, *J. Biol. Chem.* 97: 549, 1932.
10. Myers, V. C.: Creatine and Creatinine, *Yale J. Biol. & Med.* 4: 467, 1932.
11. Rose, W. C., Helmer, O. M., and Chanutin, A.: A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissues, *J. Biol. Chem.* 75: 543, 1927.
12. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1928, ed. 2, p. 107, Oliver and Boyd.

DIABETES AND CORONARY THROMBOSIS*

AN ANALYSIS OF CASES WHICH CAME TO NECROPSY

MORRIS ENKLEWITZ, M.D.

NEW YORK, N. Y.

MANY reports dealing with the vascular complications of diabetes have recently been published. Of the 1,784 deaths of diabetic individuals in New York City in 1930,¹ more than half were due to cardiovascular-renal disease. Particular emphasis has been laid upon the frequent association of diabetes and coronary disease. In his excellent monograph, Levine² states that diabetes has a most important bearing on the development of coronary thrombosis.

Because abundant clinical and post-mortem material was available, it was decided to review our records and compare results with those of other observers. Only cases which came to necropsy were studied.

GROUP I

Ninety-two cases of diabetes were analyzed as to age, sex, and coronary artery pathology. The latter was divided into thrombosis with infarction, thrombosis alone, and slight, moderate and marked sclerosis. The results are shown in Table I.

TABLE I

AGE	THROMBOSIS WITH INFARCT	THROMBOSIS ALONE	CORONARY SCLEROSIS			NEGATIVE	TOTAL
			SLIGHT	MODERATE	MARKED		
10-19						1	1
20-29						1	1
30-39						3	3
40-49	1		2	3		5	11
50-59	8		3	6	7	4	28
60-69	8	4	7	7	7	2	35
70-79	5			2	5	1	13
Total	22	4	12	18	19	17	92

There were 26 cases of thrombosis with or without infarction (28 per cent). Twenty of the 26 occurred in the 50-69 year age group. The average age of these 20 was 61 years. Thirteen were male and 7 female.

There were 16 cases under the age of 50 years. Only one of these showed occlusion; 10 showed no pathological changes in the coronary arteries.

*From the Medical Division of Montefiore Hospital, New York City.

The average age of the entire group was 58.5 years. The average duration of the diabetes was 7 years.

There were 19 patients with gangrene of the extremities, all over the age of 50 years. Nine had occlusion and 6 marked sclerosis of the coronary vessels. This would tend to confirm the clinical impression that cases with gangrene are very likely to have severe coronary disease.

GROUP II

For the purpose of comparing age and sex a group of 96 nondiabetic cases with the pathological diagnosis of coronary artery disease was then studied. The results are shown in Table II.

TABLE II

AGE	THROMBO- SIS WITH INFARCT	THROMBO- SIS ALONE	CORONARY SCLEROSIS			TOTAL
			SLIGHT	MOD- ERATE	MARKED	
20-29		1				1
30-39				1		1
40-49	4	3	2	1	2	12
50-59	15	2		2	4	23
60-69	34	4		2	7	47
70-79	6	1		1	2	10
80-		1			1	2
Total	59	12	2	7	16	96

Of the 71 cases of thrombosis with or without infarction, 55 occurred in the 50-69 year age group. The average age of these 55 was 61 years; ten were female.

The average age of the entire group was 60 years.

Both groups are compared in Table III.

TABLE III

		DIABETIC	NONDIABETIC
50-69 Years	Total number cases	92	96
	Average age	58.5	60
	Number with occlusion	26	71
	Number of cases	63	70
	Number with occlusion	20	55
	Average age (occlusion)	61	61
	Males (occlusion)	13	45
	Females (occlusion)	7	10
	Per cent females	35	18

It is evident that the majority of all our cases occurred between the ages of 50 and 69 years. Here, too, were found the greatest number with occlusion.

The average age of both groups was about the same, and was exactly the same in the cases of occlusion occurring in the 50-69 year age group.

Occlusion occurred more frequently in diabetic than in nondiabetic females (35 to 18 per cent).

GROUP III

One hundred diabetics past the age of 40 years were studied to determine the extent of vascular changes in heart, kidneys, aorta and extremities. Results are shown in Table IV.

TABLE IV

	CASES
Coronary occlusion	34
Coronary sclerosis	45
Atherosclerosis of aorta	79
Arteriosclerosis and arteriolosclerosis of kidneys	70
Gangrene of extremities	19
Hypertension	44

Levine² found that 34, or 23.7 per cent, of a total of 145 cases of coronary occlusion had diabetes or glycosuria. Twelve of the 34 were females (35 per cent). Of the remaining 111 nondiabetics, 22 were females (about 20 per cent). Here our figures agree quite closely. The average age of his diabetics was 58.1 years, and for the entire group it was 57.8 years.

Warren³ examined the hearts of 282 diabetic cases and found 34 cases of thrombosis with infarction. Nine were fresh, 18 healed and 7 fresh and healed. For the 18 cases of healed infarcts, the average duration of the diabetes was 12.5 years and the average age 63.7 years.

Gibb and Logan⁴ in reviewing 147 diabetic autopsies found myocardial infarction in only 11 cases, all in patients over the age of 40 years.

Among 55 autopsied diabetics Root⁵ found coronary sclerosis in 33 cases.

Wilder⁶ examined the hearts of 49 diabetic patients who came to post-mortem examination and found that 17, or 34 per cent, showed coronary sclerosis.

Of 77 necropsies on diabetic patients, Blotner⁷ reports that 35, or 45 per cent, showed abnormal coronary vessels. Coronary thrombosis occurred in 8, or 23 per cent, of the 35 cases. Twenty-eight of the 35 cases were in the sixth, seventh and eighth decades.

Warren and Root⁸ report their findings in 26 autopsied cases of diabetes. Ten, all over the age of 48 years, had coronary sclerosis. Of 17 patients over 40 years, 4 had myocardial infarcts and 5 extreme sclerosis of the coronary vessels.

Nathanson⁹ reviews 100 necropsies of patients who had suffered from diabetes. Of 26 below the age of 50 years only 2 show coronary disease. Of 74 cases over 50 years, 39, or 52 per cent, show coronary involvement.

GROUP IV

To determine the relative frequency with which coronary occlusion occurs in diabetics and nondiabetics, we reviewed 594 consecutive autopsied cases whose ages ranged between 50 and 69 years. The results are shown in Table V.

TABLE V

	DIABETIC	NONDIABETIC
Number of cases	74	520
Number with coronary occlusion	23	77
Percentage with coronary occlusion	31	16

Of 100 cases with coronary occlusion, 23 were diabetic. This compares favorably with Levine's² 23.7 per cent. The incidence of occlusion was twice as great in our diabetic group. We fully recognize the dangers of comparing so small a group with the much larger nondiabetic group. However, we feel quite certain that coronary occlusion is more common in diabetics. Blotner⁷ reports an incidence of 45 per cent in diabetics as compared with 21 per cent in nondiabetics above the age of 40 years. His findings relate only to coronary sclerosis. Nathanson⁹ gives the following figures for individuals past the age of 50 years: coronary disease in diabetics 52 per cent; in nondiabetics 8 per cent.

The greater incidence of coronary disease in diabetic as compared with that in nondiabetic women may be explained partly by the more frequent occurrence of diabetes in females. Wendt and Peck¹⁰ studied 1,073 cases of diabetes and found among them twice as many females as males. This was particularly true of the group between 40 and 60 years.

DISCUSSION

Even if it is granted that the older diabetic patient presents the picture of extensive vascular degeneration, it does not at all follow that diabetes is an etiological factor in the production of atherosclerosis. Indeed, one might offer this as proof, with equal justification, that diabetes is a manifestation of atherosclerosis. The introduction of insulin has caused us to alter many ancient concepts concerning diabetes. Yet the dogma that the abnormal metabolism found in diabetic individuals favors or hastens the production of atherosclerosis is as widely adhered to as ever. When one examines the scanty evidence upon which this belief is founded, one cannot help but marvel at the universal acceptance accorded this view.

Joslin¹¹ has championed the Aschoff modification of Virchow's imbibition theory of arteriosclerosis. It is believed that there is a fatty deposition in the wall at the site where vessels are under physiological strain. The fats are derived from the greater concentration of lipoids,

especially cholesterol esters, in the plasma. Joslin¹² states that the evidence implies that the increasing incidence of arteriosclerosis in the diabetic individual can be checked and the earlier types of arteriosclerosis can be overcome by a diet which provides for the complete oxidation of fat. In a recent paper by Joslin¹³ it is most interesting to read that "one would like to say that arteriosclerosis could be avoided or at least postponed if the cholesterol in the blood as a representative of all the lipids could be kept normal; and this may be true, but the evidence is insufficient."

Moscheowitz¹⁴ believes that arteriosclerosis is due to circulatory stress such as is caused by hypertension. He states that an increasing doubt has arisen as to whether experimental cholesterol arteriosclerosis represents human arteriosclerosis.

Despite the fact that excess of cholesterol of the blood is an exception in uncomplicated diabetes in children,¹⁵ attempts have been made to establish the presence of premature arteriosclerosis in the young diabetic patient. Since death in the latter is a rarity, investigators have had to resort to radiographic methods to demonstrate calcification of the vessels of the lower extremities. Morrison and Bogan¹⁶ reporting from Joslin's clinic found that 53 per cent of 324 diabetic patients showed calcification of the vessels of the lower extremities. Critical analysis of their tables reveals, however, that of 121 cases under the age of 40 years, only 5 are positive. There are 25 patients under the age of 40 years who have had diabetes for 5 years or longer, and only 3 of these show calcified vessels. Calcification was most marked in the fifth to the eighth decades.

Reporting also from Joslin's clinic, Shepardson¹⁷ examined 50 cases of patients under the age of 40 years who had had diabetes for 5 years or more. Eighteen, or 36 per cent, showed radiographic evidence of calcified vessels, an astonishingly high figure. We find it difficult to reconcile her results with those of Morrison and Bogan, particularly as both report from the same clinic.

White and Hunt¹⁵ found that 9 of 48 diabetic children had x-ray evidence of arteriosclerosis.

Bowen and Koenig¹⁸ report on 58 cases in which the diabetes had been unprotected with insulin for less than 5 years. Seventeen showed calcification of the vessels of the feet. Fourteen of these 17 occurred in the sixth, seventh and eighth decades. Of their 58 cases there were 20 under the age of 40 years, and but one of these showed calcification.

From the above it can be seen that advocates of the premature arteriosclerosis theory cannot agree among themselves. In addition there is lacking adequate data on the vessels of normal controls under the age of 40 years. If arteriosclerosis be present to the extent that some would have us believe, why is not gangrene seen in the young diabetic patient?

Valuable information can be obtained from examining the eyegrounds of diabetic patients. The retinitis found in diabetes is the retinitis of arteriosclerosis.¹⁹ Of 44 patients with retinal disease reported by Wagner and Wilder²⁰ all but two were more than 40 years old. Of these two, one had nephritis and the other hyperemia of the optic nerve which probably had no connection with the diabetes.

Spalding and Curtis²¹ investigated 307 cases of diabetes and found that 207, or 67 per cent, had no abnormalities of the retina. Included in these are 17 children under 16 years of age. Forty-six, or 15 per cent, showed retinal arteriosclerosis with no other changes; 16, or 5 per cent, had retinitis, all showing arteriosclerosis of the retinal vessels as well. Ten of the 16 had peripheral arteriosclerosis also. Hypertension was a consistent finding in cases with retinal arteriosclerosis and retinitis. The authors regard the retinitis found in diabetes as that of hypertensive cardiovascular disease. Of their 16 cases with retinitis, 75 per cent had hypertension and impaired renal function. If diabetes causes premature atherosclerosis, why is not retinitis seen in the young diabetic patient?

One is likely to lose sight of the frequency with which hypertension occurs in the older diabetic. Forty-four of one hundred cases past the age of 40 years had hypertension. When one considers that there were 34 cases of coronary occlusion in the hundred, one can well suspect that the incidence of hypertension was at one time much greater. Fishberg²² calls attention to the fact that the older diabetic patient is very liable to have essential hypertension. The same author comments that in some cases of essential hypertension with diabetes it is possible that pancreatic arteriolosclerosis, due to the hypertension, is responsible for the disturbance in carbohydrate metabolism. Joslin²³ found that 33 per cent of his older diabetic patients had hypertension. Kramer²⁴ found hypertension in 39 per cent of 500 diabetics. He attributes both hypertension and diabetes to a common cause. He states that a pre-existing hypertension produces changes in the vessels of the pancreas and this in turn reacts upon the activity of the islands of Langerhans. Major²⁵ found the systolic blood pressure of elderly diabetic patients higher than that of normal controls. That hypertension is an important factor in the production of coronary disease is generally admitted. Levine² ranks it first as an etiological cause. Fishberg²² states that the large majority with essential hypertension develop arteriosclerotic changes of the coronary arteries.

If hypertension is so important in the production of coronary atherosclerosis and if hypertension is so frequently encountered in the older diabetic, why is it necessary to invoke diabetes as a causative factor?

The pancreas is frequently involved in arteriosclerosis. In describing the distribution of arteriolosclerotic lesions Fishberg²² lists the kidney first and the spleen, pancreas, liver and brain next in the order of

frequency of occurrence. Discussing the nature of the disease, he regards the changes in the arterioles as a manifestation of the wear and tear to which they have been subjected.

Barron²⁶ made careful post-mortem studies of the pancreas in cases of coronary sclerosis and found advanced atherosclerosis of the pancreatic arteries. He believes pancreatic atherosclerosis to be a relatively common condition associated with cases of advanced hypertension and with coronary sclerosis. The diabetes in these cases is probably due almost entirely to this lesion.

Eighteen of Warren and Root's⁸ 26 autopsied diabetic cases showed arteriosclerosis of the pancreatic vessels.

Evidence of vascular involvement of other organs is frequently found in the aged diabetic patient. Of our hundred cases past the age of 40 years, 79 had generalized atherosclerosis; 70 had arterio- and arteriosclerosis of the kidneys; 19 had gangrene of the extremities; and 11 had cerebral arteriosclerosis. Joslin²⁷ calls attention to the occurrence of peptic ulcer in 30 of his cases. Jankelson and Rudy²⁸ report 6 cases of diabetes with ulcer. All but one were in patients over 50 years old. Ophüls²⁹ has described the relation of peptic ulcer to arteriosclerosis. He says, "In studying arteriosclerosis the rather common occurrence of gastric or duodenal ulcer in arteriosclerotics became so evident that almost unconsciously I began to look on it as a lesion comparable to arteriosclerotic scars in heart and kidney." To which we add, "and pancreas."

If diabetes be related to coronary disease, the latter should be found quite commonly in the young diabetic patient, for it is here that the metabolic disorder is most severe. Before insulin days these young people died too soon after the onset of their symptoms to permit the development of pathological changes in other organs. It is now ten years since the introduction of insulin, and the young diabetic patient continues to live and thrive. During this period a fairly large number should have died of coronary disease. Only a few such cases have been described. Warren³ reports a patient who had diabetes for eight years and died at the age of thirty-three years of coronary disease. He also mentions a personal communication relating to a diabetic patient who died at twenty-two years of coronary thrombosis.

Coronary thrombosis may occur in young nondiabetic persons. Smith and Bartels³⁰ report two cases of coronary thrombosis in nondiabetic persons aged thirty-five and thirty-six years. They review 21 cases previously reported, all under the age of 40 years, with ages ranging from 12 to 39 years. Sutton and Brandes,³¹ reviewing 340 nondiabetic cases which came to necropsy and in which gross coronary sclerosis was found, comment on the early age at which definite arteriosclerotic changes were disclosed. The youngest was 5 years old, and in a boy of 12 years definite gross sclerosis of the large coronary arteries was

evident. They found 42 cases of coronary sclerosis in the second, third and fourth decades. We attach great significance to the fact that the young diabetic person has done so splendidly, for it is perhaps the best proof that he has not developed atherosclerosis prematurely.

Warren³ calls attention to the long duration of the diabetes before the onset of coronary symptoms. He states that proof that the diabetes is not merely an incidental feature in these cases is to be found in the diabetic process long antedating the cardiac condition. Several objections to this are obvious. Urinalysis is part of a routine physical examination; an electrocardiogram is not. Coronary disease may be present for a long period and yet give no signs or symptoms until myocardial ischemia develops. Even under these circumstances the electrocardiogram (as interpreted in the past) may reveal nothing. Diabetes lends itself much more readily to detection than does coronary disease.

Based on his material, Leutenegger³² states that he cannot demonstrate that there exists a special diabetic arteritis characterized by frequency or prematurity. In his cases the vascular changes clinically occur in the sixth and seventh decades, in the same age group in which vascular changes are most common in the nondiabetic person as well.

Gray and Sansum³⁵ note a low incidence of arteriosclerosis in their series before the fifth decade, even in cases where the diabetes is of long duration. They find arteriosclerosis to be more closely related to the age of the patient than to the duration of the diabetes.

Nathanson⁹ believes that at the present time it does not seem justifiable to conclude that diabetes is a causative factor in the production of arteriosclerosis, as no mechanism for this process has been satisfactorily proved.

Cruikshank³³ states that it is considered more probable that these two conditions result from a common cause (vascular degeneration) than that the glucosuria is an etiological factor in the production of coronary thrombosis.

John³⁴ regards the diabetes occurring in middle age as comparable to the failure of other functions in the body resulting in heart and kidney disease and hypertension. The effect of age upon carbohydrate tolerance is well known. In this connection, the work of Marshall³⁶ is worthy of mention. This investigator studied glucose tolerance in a series of men whose average age was 72 years. In a group of healthy old men he found that 14 per cent had normal blood sugar curves and 14 per cent had typical diabetic curves. In a group of "unhealthy" subjects suffering from chronic bronchitis, arthritis, cancer, etc., he found that 14 per cent had normal curves and 50 per cent had diabetic curves. The others had atypical sugar tolerance curves. He also studied 5 individuals who were grossly senile and found that 3 of these had diabetic curves. Commenting on the high incidence of diabetic

curves, he states that this can be regarded as indicative of the marked disturbance of the carbohydrate mechanism which may occur in a certain proportion of aged people.

We prefer to regard diabetes in people past the age of 40 years as a manifestation of degenerative vascular disease. By so doing, we very properly minimize the metabolic disorder and stress the condition of the vascular tree. If diabetes of middle age is interpreted as clinical evidence of generalized arteriosclerosis, it is reasonable to expect that a large number of diabetic patients will also have coronary artery disease.

SUMMARY

1. Twenty-six of 92 diabetic patients showed coronary thrombosis. Twenty cases of coronary artery thrombosis occurred in the sixth and seventh decades.

2. Coronary thrombosis occurred more frequently in the diabetic than in the nondiabetic female patient.

3. In both diabetic and nondiabetic patients coronary thrombosis occurred predominantly in the sixth and seventh decades.

4. Of 100 diabetic patients past the age of 40 years, 34 showed coronary thrombosis and 45 coronary sclerosis. Seventy-nine had atherosclerosis of the aorta. Seventy showed arteriosclerosis and arteriosclerosis of the kidneys. Nineteen had gangrene of the lower extremities. Hypertension was present in 44 cases.

5. Coronary thrombosis occurred twice as frequently in diabetic as in nondiabetic patients.

6. The opinion is expressed that both coronary thrombosis and diabetes in individuals over the age of 40 years are manifestations of degenerative vascular disease.

REFERENCES

1. Causes of Death in Diabetics at Various Ages, Bull. Dept. of Health, N. Y. C. 20: 357, 1931.
2. Levine, S. A.: Coronary Thrombosis, *Medicine* 8: 253, 1929.
3. Warren, S.: Pathology of Diabetes Mellitus, Philadelphia, 1930, pp. 144-146, Lea & Febiger.
4. Gibb, W. F., and Logan, V. W.: Diabetes Mellitus. A Study of 147 Autopsies, *Arch. Int. Med.* 43: 367, 1929.
5. Root, H. F.: Arteriosclerosis in the Legs and Heart in Diabetes, *N. Y. State J. Med.* 28: 1287, 1928.
6. Wilder, R. M.: Necropsy Findings in Diabetes, *Southern M. J.* 19: 241, 1926.
7. Blotner, H.: Coronary Disease in Diabetes Mellitus, *New England J. Med.* 203: 709, 1930.
8. Warren, S., and Root, H. F.: Pathology of Diabetes, *Am. J. Path.* 1: 415, 1925.
9. Nathanson, M. H.: Coronary Disease in 100 Autopsied Cases, *Am. J. M. Sc.* 183: 495, 1932.
10. Wendt, L. F., and Peck, F. B.: Diabetes Mellitus. A Review of 1,073 Cases, *Am. J. M. Sc.* 181: 52, 1931.
11. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, 1928, 4th ed., p. 689, Lea & Febiger.

12. Idem: Arteriosclerosis and Diabetes, *Ann. Clin. Med.* 5: 1061, 1927.
13. Idem: An Appraisal of the Present Treatment of Diabetes, *J. A. M. A.* 97: 596, 1931.
14. Moschcowitz, E.: The Cause of Arteriosclerosis, *Am. J. M. Sc.* 178: 244, 1929.
15. White, P., and Hunt, H.: Cholesterol of the Blood of Diabetic Children, *New England J. Med.* 202: 607, 1930.
16. Morrison, L. B., and Bogan, I. K.: Calcification of the Vessels in Diabetes, *J. A. M. A.* 92: 1424, 1929.
17. Shepardson, H. C.: Arteriosclerosis in the Young Diabetic Patient, *Arch. Int. Med.* 45: 674, 1930.
18. Bowen, B. D., and Koenig, E. C.: Arteriosclerosis and Diabetes, *Bull. Buffalo Gen. Hosp.* 5: 31, 1927.
19. Moore, R. F.: Retinitis of Arteriosclerosis, *Quart. J. Med.* 10: 29, 1916-17.
20. Wagener, H. P., and Wilder, R. M.: The Retinitis of Diabetes Mellitus, *J. A. M. A.* 76: 515, 1921.
21. Spalding, F. M., and Curtis, W. S.: Retinitis and Other Changes in the Eyes of Diabetics, *Boston M. & S. J.* 197: 165, 1927.
22. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, 1931, 2nd ed., pp. 486, 525, Lea & Febiger.
23. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, 1923, 3rd ed., p. 578, Lea & Febiger.
24. Kramer, D. W.: Hypertension and Diabetes, *Am. J. M. Sc.* 176: 23, 1928.
25. Major, S. G.: Blood Pressure in Diabetes Mellitus, *Arch. Int. Med.* 44: 797, 1929.
26. Barron, M.: Diseases of the Pancreas, *Arch. Int. Med.* 35: 807, 1925.
27. Joslin, E. P.: See reference 11, p. 716.
28. Jankelson, I. R., and Rudy, A.: The Simultaneous Occurrence of Peptic Ulcer and Diabetes or Glycosuria, *Am. J. M. Sc.* 181: 356, 1931.
29. Ophüls, W.: The Relation of Gastric and Duodenal Ulcer to Vascular Lesions, *Arch. Int. Med.* 11: 469, 1913.
30. Smith, H. L., and Bartels, E. C.: Coronary Thrombosis With Myocardial Infarction and Hypertrophy in Young Persons, *J. A. M. A.* 98: 1172, 1932.
31. Sutton, D. C., and Brandes, W. W.: Arteriosclerosis of the Coronary Arteries, *J. Lab. & Clin. Med.* 16: 1185, 1930-31.
32. Leutenegger, F.: Diabetes Mellitus and Gefäßsystem, *Ztschr. f. Klin. Med.* 119: 164, 1931.
33. Cruickshank, N.: Coronary Thrombosis and Myocardial Infarction With Glycosuria, *Brit. M. J.* 1: 618, 1931.
34. John, H. J.: Diabetes. A Statistical Study of 1,000 Cases, *Arch. Int. Med.* 39: 67, 1927.
35. Gray, P. A., and Sansum, W. D.: The Higher Carbohydrate Diet Method in Diabetes Mellitus. Analysis of 1,005 Cases, *J. A. M. A.* 100: 1580, 1933.
36. Marshall, F. W.: The Sugar Content of the Blood in Elderly People, *Quart. J. Med.* 24: 257, 1930-31.

THE BLOOD PRESSURE OF CHINESE LIVING IN EASTERN CANADA*

A. KRAKOWER, M.D.
MONTREAL, CAN.

A STUDY of blood pressure in groups of people of different races and nationalities is of importance in setting standards of normal averages among them. It also serves to reveal the incidence of hypertension as well as the influence of such factors as environment, mode of living and heredity on the height of systolic and diastolic blood pressure. Arterial hypertension—so common in civilized countries, particularly in the temperate zone—is of quite infrequent occurrence in China (Cadbury,¹ Cruickshank,² Kilborn,³ Foster⁴). It is generally recognized, too, that the blood pressure of Chinese living in China is at a lower level than the accepted standards for Americans and Europeans. Reports in the literature show that this is true for different sections of that densely populated country.

LITERATURE

Cadbury¹ found in a series of healthy Cantonese (South China) students that the systolic pressure averages 20-30 mm. Hg less and the diastolic 10-20 mm. lower than the standards for European and American men of corresponding age, weight and height. The analysis of the records of natives living in Northern China by Tung,⁵ showed a mean systolic of 102 mm. for the ages fifteen to nineteen years, and 113 mm. for fifty to fifty-four years, with a corresponding rise in the diastolic from 64 to 73 for the same age periods. Kilborn³ examined 700 Szechwanese (West China) students and obtained a mean systolic pressure of 111 mm. and diastolic of 70 mm. Similarly, Ying⁶ in a report of a smaller group living in Chekiang (East Central China) obtained average figures of 110-118 with a rise above 125 mm. for groups over fifty years of age. In contrast to these studies are the observations of Alvarez,⁷ who in 6,000 healthy American men ranging in age from sixteen to forty years found an average systolic blood pressure of 129 mm.

It is generally accepted that the pressure of normal adults of Anglo Saxon origin is about 120-125 mm. and diastolic 80-85 mm. (Symonds,⁸ Woley⁹), although somewhat higher readings are still considered normal. Thus Hunter and Frost's¹⁰ statistics show that the average normal systolic pressure varies from 120 to 135 and diastolic from 80 to 89 for the ages twenty to sixty years. In contrasting blood pressures of Chinese

*From the University Clinic, Department of Medicine, McGill University and Royal Victoria Hospital, Montreal, Canada.

and Americans, the evidence therefore seems to show that the former's level is consistently about 10-15 mm. lower than that of the latter. Another interesting fact is revealed in the influence of environment on the height of blood pressure. Tung¹¹ recorded the pressure of 30 Chinese students in America and again in Peking three years later. An average drop of 11 mm. in systolic and 8 mm. in diastolic was noted after their return to China. In 58 Americans studied in the same way, this author¹² showed that a distinct decrease in blood pressure occurs in Westerners residing in China. Foster⁴ came to the same conclusion, for in a group of 120 Americans living in Hunan, he found that the average pressure approached that of the local Chinese population. With these observations in mind, it seemed of interest to investigate a group of Chinese living in Canada in order to determine their average blood pressure. Such a study would also indicate the frequency of arterial hypertension among them.

PROCEDURE

Two hundred and thirty-nine Chinese living in the city of Montreal, whose ages range from seven to sixty-nine years (Table I) form the basis of this report. Only 4 females are included because of the small number of Chinese women in the local colony. Practically all Chinese in this community came originally from Canton and the immediate neighborhood in the south of China. The majority have lived here for many years with only occasional brief visits to China. Many of them have become thoroughly acclimatized to our Western civilization. Their occupations (Table II) are for the most part manual labor in laundry or kitchen.

TABLE I
AGE DISTRIBUTION OF 239 CANADIAN CHINESE

AGES	NUMBER OF SUBJECTS
5-9 years	3
10-19	8
20-29	31
30-39	50
40-49	81
50-59	54
60-69	12

Most of the blood pressure records were taken during the week-ends, when the Chinese assemble for diversion and amusement. All readings were done by the author and in the mid-afternoon or early evening. A standard mercury sphygmomanometer was used with a 12 cm. cuff. The beginning of the first and fourth phases was regarded as systolic and diastolic pressure respectively. The subjects sat comfortably in a chair, resting one arm on an adjoining table. With a few exceptions, they had not worked immediately before the recording of the pressure. The Chinese are rather phlegmatic and on that account did not manifest un-

due nervousness at the procedure. In each case information was elicited relating to the duration of residence in Canada, the number of visits to China, age, height, weight and occupation. The heights and weights are necessarily approximate because there was no opportunity to corroborate

TABLE II
OCCUPATIONS OF 239 CANADIAN CHINESE

Laundry worker	-	101 (42.2%)
Cook	-	35
Merchant	-	30
Restaurant owner	-	22
Student	-	11
Housewife	-	3
Waiter	-	2
Teacher	-	2
Taxi driver	-	2
Physician	-	1
Tailor	-	1
Barber	-	1
Engineer	-	1
Clerk	-	1
Unemployed	-	16
Not recorded	-	10
Total	-	239

these measurements. When the first blood pressure reading was found to be 140 mm. (systolic) or over, the subject was instructed to rest quietly while sitting in the chair and the reading repeated after five minutes. The blood pressure was checked in these instances because of the well-known tendency of nervousness and excitement to cause a rise in systolic pressure. In several instances three consecutive readings were made in the same subject. In a number of normal individuals, and particularly in those with hypertension, the heart was examined for evidence of valvular disease and enlargement. The pulse rate and presence or absence of peripheral arteriosclerosis were noted as frequently as possible.

OBSERVATIONS

Blood Pressure and Duration of Residence in Canada.—The majority of the Chinese in Montreal have been living here for ten years or longer; therefore one cannot correlate the height of the blood pressure with the length of time they have been residing here. Thus only 4 subjects have been in this country less than five years, and 8 between six and nine years. Ninety-one have been residents of Canada for from ten to nineteen years and 116 have been here for more than twenty years. The average for all cases, excluding those born in Canada, is nineteen and one-half years. It may be mentioned, however, that the more recent immigrants do show a distinct tendency toward hypotension. Thus a male, aged forty-three years, in Canada three years, has a blood pressure

of 78/58; another, aged thirty-six years, in Canada four years, has a blood pressure of 102/66; and a third, a young Chinese physician aged twenty-five years, in Canada also for four years, was observed to have a pressure of 104/84.

TABLE III

RELATION OF BLOOD PRESSURE TO HEIGHT AND WEIGHT IN 20 CANADIAN-BORN CHINESE

SEX	AGE (YR.)	HEIGHT (CM.)	WEIGHT (KILOS)	BLOOD PRESSURE SYST. & DIAST.
Male	10	111.7	30.4	104 : 76
Male	24	162.5	60.0	126 : 80
Male	7	----	20.4	110 : 84
Male	10	----	32.2	116 : 74
Male	9	----	25.0	112 : 78
Female	31	154.9	60.0	112 : 78
Female	7	99.0	20.0	98 : 66
Female	20	160.0	50.0	122 : 74
Male	33	167.7	74.5	120 : 94
Male	16	167.7	52.2	128 : 79
Male	22	171.4	55.9	116 : 78
Male	22	171.4	56.3	125 : 82
Male	23	175.3	61.8	116 : 88
Male	28	165.1	61.3	116 : 86
Male	18	170.2	84.0 (obese)	124 : 86
Male	14	152.4	35.9	112 : 78
Male	18	162.5	----	124 : 92
Male	17	170.2	55.0	122 : 78
Male	34	162.5	59.0	116 : 74
Male	14	152.4	60.00 (overweight)	124 : 96
Average systolic = 117.1 mm.				
Average diastolic = 81.0 mm.				

Blood Pressure in Canadian-Born Chinese.—Twenty individuals are included in this category, and Table III shows the relation of their blood pressure to height and weight. All have normal pressures, and when averaged the systolic equals 117.1 mm. and the diastolic 81.0 mm. When we compare these figures with those reported in native Chinese of similar age periods, we find that the Canadian subjects have definitely higher systolic and diastolic pressures. The average blood pressure in this latter group is lower than that obtained for the series of 239 cases, but the two are not comparable because the Canadian-born subjects number only 20 in all and are predominantly in the younger age periods of life.

The Average Blood Pressure for Different Ages.—A comparison of the mean or average blood pressure obtained in our group with that reported by Ying⁶ for similar age periods is shown in Table IV. It is obvious that the average systolic pressure of Chinese living in Canada is distinctly higher (by about 10 mm.) for each decade than that for natives living in China, especially in young and middle-aged adults. In both a slight but steady increase in pressure occurs with advancing age and in the later decades (fifty to sixty-nine years) there is a sharp rise which almost reaches 140 mm. In our subjects this may be accounted for by the greater frequency of hypertension in the older men.

Thus for the ages fifty to sixty-nine years, 21 subjects had systolic pressures above 140 mm., whereas in the earlier decades there were only 14 above this level. This is even more striking when we bear in mind the fact that the 21 cases with hypertension occurred in a total of 66 subjects while the 14 younger hypertensives were found in 173 subjects. The average pressure in Canadian Chinese is in fact the same as that for white people of similar ages, living on this continent (Alvarez,⁷ Symonds,⁸ Woley⁹). The same conclusions hold true for the averages of diastolic pressure, though there is not such a significant rise with advancing age. Table IV shows that the average diastolic pressures of Canadian Chinese are higher than those of their compatriots residing in China.

TABLE V

RELATION OF SYSTOLIC BLOOD PRESSURE TO AGE IN 239 CHINESE

PRESSURE IN MM.	AGE IN YEARS							TOTAL
	5-9	10-19	20-29	30-39	40-49	50-59	60-69	
70- 79					1			1
80- 89					1			1
90- 99	1				2	1		4
100-109		1	4	8	10	1		24
110-119	2	2	9	13	13	8	1	48
120-129		5	12	12	28	11	3	71
130-139			5	12	18	16	4	55
140-149			1	2	3	6	1	13
150-159				2	1	1	1	5
160-169					3	3	2	8
170-179				1		3		4
180-189								0
190-199						2		2
200-209					1	1		2
210-219						1		1
Total	3	8	31	50	81	54	12	239

Relation of Systolic and Diastolic Blood Pressure to Age.—The levels of systolic and diastolic blood pressure for each decade are shown in Tables V and VI respectively. The majority of our cases (185 or 77.4 per cent) are in the age group between thirty and fifty-nine years: One hundred and seventy-four subjects (72.8 per cent) have systolic blood pressures ranging between 110 and 139 mm., whereas in 35 (14.6 per cent) the reading is above 140 mm. The largest single group of 71 cases occurs in the 120-129 mm. division. It is seen how few cases actually have pressures below 110 mm., thus explaining the higher mean pressure of Western Chinese as compared to those living in China. In the distribution of the diastolic records, 166 subjects (70.0 per cent) have readings below 90 mm., of which 76 have a pressure of 80-89 mm. In 20 (8.4 per cent) a pathological reading of over 100 mm. was found. Here, too, really low figures are relatively uncommon in the diastolic pressures of Canadian Chinese.

TABLE VI
RELATION OF DIASTOLIC BLOOD PRESSURE TO AGE*

PRESSURE IN MM.	AGE IN YEARS							TOTAL
	5-9	10-19	20-29	30-39	40-49	50-59	60-69	
40- 49				1		1		2
50- 59					2			2
60- 69	1		1	6	6	1	1	16
70- 79	1	5	9	21	23	10	1	70
80- 89	1	1	16	5	27	21	5	76
90- 99		2	4	12	16	14	3	51
100-109			1	3	3	2	2	11
110-119				2	2	4		8
120-129								0
130-139						1		1
Total	3	8	31	50	79	54	12	237

*In 2 subjects diastolic pressure could not be recorded, the sound disappearing shortly after the onset of the first (systolic) phase.

Blood Pressure and Obesity.—In a study of this kind, it is difficult to define precisely where obesity begins. It is generally agreed, however, (McLester,¹³ Harrop¹⁴) that an excess of 25 per cent or more above the standard or ideal weight for age and height is to be considered abnormal. But many persons are found who are 20 pounds (9.0 kilos) or more above their ideal weight and these fall into the overweight class. Of our 239 Chinese, 11 were observed to be distinctly obese, and 12 were included in the second group of overweight individuals, giving a total of 23 or 10 per cent in the obesity group. In common with white people, the later decades are subject to obesity; thus 8 of the obese Chinese were in the fourth decade of life, 3 in the fifth and 9 in the sixth decade. When we come to examine the blood pressures of these, we find that 5 obese subjects have arterial hypertension; i.e., a systolic blood pressure above 140 mm., and 6 have diastolic pressures over 100 mm. There is therefore in this small group of overweight Chinese a higher incidence of hypertension (21.7 per cent) than in those of normal or average weight (10.1 per cent). This is in agreement with what is generally found, viz., that high blood pressures occur with greater frequency in those who are obese than in those who are not (Alvarez and Stanley,⁷ Symonds,⁸ Hartman and Ghrist¹⁵). It should be added that the diet of Canadian Chinese is a liberal one and moderately well balanced. In China the natives subsist largely on a vegetable diet.

Hypertension in Chinese.—A systolic pressure of 140 mm. Hg is usually regarded with suspicion at any age, and in the present study 2 consecutive readings above this level are held to be pathological and the cases included in the hypertensive group. There were 27 subjects (11.2 per cent) with such elevated pressures. It is quite possible that a number of these ought not to be considered hypertensive in view of the well-known effect of nervousness and apprehension in producing a rise of systolic pressure. And though most of the Chinese did not mani-

fest any uneasiness, yet the procedure of taking blood pressure was a strange one to many. As mentioned before, a five-minute rest interval was allowed between the first and second reading to remove as much of the nervous factor as possible. A number had undoubted hypertension with the systolic just below or above 200 mm., and in 13 subjects the diastolic was over 100 mm. In 14 cases the heart was examined, and in 6 of these there was confirmatory evidence of hypertensive disease manifested by cardiac enlargement and accentuation of the second aortic sound at the base. In one subject there was a mitral insufficiency with enlarged heart and in another pronounced peripheral arteriosclerosis. In 7 no evidence of organic or valvular heart disease could be elicited by ordinary physical examination. The heart was also examined in 25 subjects whose blood pressures were within normal limits, and in 2 cases rheumatic valvular heart disease was detected. The remainder were healthy.

The frequency of hypertension in Chinese living in Canada is certainly in marked contrast to its rarity in Chinese natives. Foster¹⁶ states that among 4,000 Chinese admissions to the medical service of the Hunan-Yale Hospital in China, he was able to find less than 20 with a blood pressure of 160 or over. In his private practice in New England, however, 16 per cent of his office patients had pressures of 150 mm. or over.

The etiology of arterial hypertension remains obscure and several factors have been mentioned as contributory agents. Thus constitution, endocrine gland changes, diet, climate and mode of living have all been suggested as causes. Of these environment and mode of living deserve attention. In China, the tempo of life is certainly at a slower pace, and nervous strain, so characteristic of Western civilization, is relatively absent. Hypertension is rare among the natives, and even white people after a short residence are found to have lowered blood pressures. On the other hand, when the Chinese emigrate to this country, their blood pressures increase so that their average pressure is the same as that of the white inhabitants and hypertension is found frequently enough.

COMMENT

This work was undertaken to determine the blood pressure of Chinese living in Canada for a number of years and to compare their average pressure with that of the white inhabitants. The great majority of the subjects have been in Canada for ten years or more, and their average blood pressure is 10 mm. or more higher than that of Chinese natives for each decade. As a matter of fact, their pressures are equal to those reported for native Westerners. The astonishing finding of hypertension in 11 per cent of our subjects compared to its rarity in China, suggests the importance of the rôle of worry and

nervous strain of western life, as well as dietary and other environmental factors, in the etiology of high blood pressure. In a small number of Canadian-born Chinese the average pressure was observed to be well above that reported for Chinese natives of similar age periods, again emphasizing environment as a factor in influencing blood pressure. Obesity occurred in 10 per cent of the subjects, and in these hypertension was not uncommon. Of the 39 individuals in whom the heart was examined, 6 were found to have hypertensive heart disease and 2 rheumatic valvular disease.

SUMMARY AND CONCLUSIONS

The average blood pressure of Chinese living in Canada for ten years or more is consistently higher (10 mm. Hg) than that reported for Chinese natives. Canadian Chinese have pressures the same as those of the white population. In this series hypertension occurs with surprising frequency (11.2 per cent), in contrast to its rarity in China.

REFERENCES

1. Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, *Arch. Int. Med.* 30: 362, 1922.
2. Cruickshank, E. W. H.: Physiological Standards in North China, *China M. J.* 37: 1, 1923.
3. Kilborn, L. G.: Blood Pressure of Szechwanese Students, *China M. J.* 40: 1, 1926.
4. Foster, J. H.: Blood Pressure of Foreigners in China, *Arch. Int. Med.* 40: 38, 1927.
5. Tung, C. L.: Blood Pressure of Northern Chinese Males, *Chinese J. Physiol.* 4: 117, 1930.
6. Ying, Y. Y.: Blood Pressure of Healthy Individuals in Shaohing, *China M. J.* 40: 641, 1926.
7. Alvarez, W. C., and Stanley, L. L.: Blood Pressure in 6000 Prisoners and 400 Prison Guards, *Arch. Int. Med.* 46: 17, 1930.
8. Symonds, B.: The Blood Pressure of Healthy Men and Women, *J. A. M. A.* 80: 232, 1923.
9. Woley, H. P.: The Normal Variation of the Systolic Blood Pressure, *J. A. M. A.* 55: 121, 1910.
10. Frost, H. M.: Hypertension and Longevity, *Boston M. & S. J.* 193: 241, 1925.
11. Tung, C. L.: The Blood Pressure of Chinese in China and in the U. S. A., *Chinese J. Physiol.* rep. ser. 1: 93, 1928.
12. Idem: The Relative Hypotension of Foreigners in China, *Arch. Int. Med.* 40: 153, 1927.
13. McLester, J. S.: Nutrition and Diet in Health and Disease, Philadelphia, ed. 2, 1931, W. B. Saunders & Co.
14. Harrop, G. A., Jr.: Diet in Disease, Philadelphia, 1930, P. Blakiston's Son & Co.
15. Hartman, H. R., and Ghrist, D. H.: Blood Pressure and Weight, *Arch. Int. Med.* 44: 877, 1929.
16. Foster, J. H.: The Practice of Medicine in China and New England With Observations on Hypertension, *New England J. Med.* 203: 1073, 1930.

THE ELECTROCARDIOGRAM OF LOW VOLTAGE

A REPORT OF FIFTY AUTOPSIED CASES*

LEONARD G. STEUER, M.D.
CLEVELAND, OHIO

EVER since electrocardiography came into clinical prominence there has been an effort to correlate the height of excursion of the QRS complex or the voltage of the electrocardiogram with the functional state of the cardiac muscle. Although it has been found that some correlation exists between the extent of the voltage and the function of the heart muscle, it must be remembered that any such parallelism is indirect and subject to certain fortuitous circumstances. This is true because in the human electrocardiogram the height of the QRS complex represents a balance of electrical potential as the conduction wave passes over a complicated, interwoven mass of musculature. Notwithstanding the clinical experience of finding high voltage in patients with markedly decompensated hearts, and low voltage in hearts which are apparently functioning normally, there has been sufficient evidence to warrant looking with caution on the electrocardiogram of low voltage. The low voltage of the electrocardiogram is indicative of one of two things: either the electrical potential associated with the cardiac systole is small, or it has been neutralized by compensatory effects.

Most authorities accept an excursion of 5 mm. or less as low.^{1, 2, 3} Pardee, however, sets the lower limit of normal as 7 mm.⁴ To fall in this classification of low voltage the excursion of the QRS complex should not exceed these limits in any of the three leads of a properly standardized string. Under such circumstances it is known that low voltage may occur after acute infectious diseases or during circulatory failure of various types. Sprague and White¹ reporting on 57 cases in which the voltage was 5 mm. or less find 77 per cent of the cases related to cardiac failure either resulting from arteriosclerosis or hypothyroidism. Their series also included severe toxic or terminal myocardial states resulting from syphilitic, rheumatic or hypertensive heart disease, mediastino-pericarditis, leucemia, subacute bacterial endocarditis.

As to the prognostic significance of low voltage Hepburn and Jamieson³ report that 67.6 per cent of their patients died within six months after the first record of low voltage was taken, while 32.4 per cent were living 23.2 months after the first record of low voltage was taken.

In a series of 50 cases of low voltage reviewed by Speckman and Rich² there were 14 autopsies. In 10 instances there were enlarged hearts. In

*From the Department of Medicine, Western Reserve University, at City Hospital.

4 pericardial effusion was found, while 3 had adherent pericardium. Microscopic examination showed abnormalities of the heart muscle in every case of the 14 examined. The most frequent finding was fibrosis of the myocardium. Of this series, 32 of the patients died within six months of the first electrocardiogram of low voltage. As a result of their studies Speckman and Rich conclude that the occurrence of voltage of 5 mm. or less in a patient with heart disease is of serious prognostic importance.

Aside from the above series of autopsied cases there are few reported in the literature. The purpose of the present study is to review 50 cases of low voltage, all of which came to autopsy, and to point out the relationship between the electrocardiogram and the pathological findings. The cases presented all had electrocardiograms in which the maximum excursion did not exceed 7 mm. in a string standardized in the usual manner. All patients appeared on the wards of Cleveland City Hospital and came to autopsy in the hospital. Aside from the above mentioned requisites there was no choice of cases. The autopsy reports from the laboratory of the hospital are based on the diagnoses of several independent workers, so that a fair evaluation of the pathological material is obtained.

Of the 50 cases studied, 41 (82 per cent) were males and 9 (18 per cent) females. The average age was fifty-three years. The oldest patient was seventy-eight years and the youngest eight years. Of these 10 (20 per cent) were negro and 40 (80 per cent) were white.

Advanced cardiac failure was found in 45 of the cases (90 per cent). Cardiac decompensation was present for from two weeks to as long as seventy-two months. The average period of cardiac failure was thirteen months.

On the basis of pathological findings the cases fall into three distinct groups: those which have coronary disease as the primary cardiac lesion; those which possess a cardiac lesion complicated by coronary arteriosclerosis; those which have no involvement of the coronary arteries at all.

The group in which coronary disease is the predominating lesion comprises 21 cases (42 per cent). Table I demonstrates the degree of coronary sclerosis and the associated myocardial and electrocardiographical abnormalities. Coronary arteriosclerosis is present in this group from a moderate degree to complete occlusion with frequent thrombus formation. In several instances myocardial aneurysms are present. This group of coronary arteriosclerotic disease forms the largest single group in the series of low voltage electrocardiograms.

Group II is composed of 17 cases (34 per cent) all of which show a significant degree of coronary sclerosis, but the latter finding cannot be considered the primary lesion. There are 9 instances in this group in which luetic aortic insufficiency is the dominating cardiac abnormality. Although in these, valve leakage and subsequent myocardial fail-

TABLE I
GROUP I. CORONARY DISEASE PRIMARY FACTOR

CASE NO.	AGE	SEX	DEGREE OF CORONARY SCLEROSIS	OTHER PATHOLOGICAL FINDINGS	MAXIMUM VOLTAGE	MECHANISM	OTHER ELECTROCARDIOGRAPHIC FINDINGS
1	60	m	++	Myomalacia cordis.	6.5 mm.	Fibrillation	Splintering QRS
2	67	m	+++	Myocardial fibrosis. Nephrosclerosis.	2.0 mm.	Normal	Splintering QRS
3	73	m	+++	Myocardial fibrosis. Nephrosclerosis.	6.0 mm.	Fibrillation	T ₁ inverted deep Q ₃
4	57	m	++++	Myocardial infarct.	4.0 mm.	Fibrillation	T ₁ -T ₂ inverted
5	52	m	++++	2 cardiac aneurysms.	5.0 mm.	Normal	
6	60	m	++++	Coronary thrombosis aneurysm heart.	4.0 mm.	Fibrillation	
7	44	m	++++	Occlusion lt. descending and portion rt.	2.0 mm.	Normal	Splintering
8	58	m	++++	Adhesive pericarditis.	1.0 mm.	Normal	
9	59	m	++++	Occlusion and thrombosis. Adhesive pericarditis.	3.0 mm.	Normal	T ₁ inverted
10	47	m	+++	Aneurysm lt. ventricle.	2.0 mm.	Normal	Splintering
11	59	f	++++	Myomalacia cordis.	3.0 mm.	Normal	Splintering
12	56	m	+++	Luetic aortitis.	4.0 mm.	Normal	Arborization block
13	66	m	++++	Aneurysm lt. ventricle.	4.0 mm.	Normal	Splintering and widening QRS
14	69	m	+++	Nephrosclerosis. Marked narrowing coronary orifices.	2.5 mm.	Normal	T ₁ -T ₂ inverted
15	59	m	+++	Cor pulmonale.	5.0 mm.	Normal	Splintering
16	75	m	+++	Complete occlusion	4.0 mm.	Normal	T ₁ -T ₂ coronary type
17	78	m	+++	Occlusion right. Aneurysm heart.	2.5 mm.	Normal	Splintering QRS
18	56	m	++	Marked hyaline thickening coronary.	3.2 mm.	Normal	
19	62	m	++	Aortic stenosis, arteriosclerotic.	7.0 mm.	Normal	
20	50	m	++	Myomalacia cordis.	4.0 mm.	Normal	Splintering QRS
21	56	m	++	Arterioneurophrosclerosis.	5.8 mm.	Normal	T ₁ -T ₂ inverted

ure are the most important factors leading to death, nonetheless, the added complication of coronary sclerosis cannot be overlooked. In several instances the coronary orifices are greatly narrowed by a sclerotic process, and this must have interfered with the myocardial blood supply. Similarly there are 3 cases of mitral stenosis in this group, all of which had significant coronary arteriosclerosis. The remainder of the group, 5 cases, show nephrosclerosis, complicated by coronary arteriosclerosis. Table II demonstrates the degree of coronary sclerosis and the associated abnormalities in this group. It is of interest to note that in all cases in which hypertension plays a part, coronary sclerosis is also present.

TABLE II

GROUP II. CORONARY DISEASE COMPLICATING OTHER CARDIAC LESIONS

CASE NO.	AGE	SEX	DEGREE OF CORONARY SCLEROSIS	OTHER PATHOLOGICAL FINDINGS	MAXIMUM VOLTAGE	MECHANISM	OTHER ELECTROCARDIOGRAPHIC FINDINGS
22	63	m	++	Luetic aortitis with ring involvement.	3.0 mm.	Nodal	Splintering
23	73	m	++	Luetic aortic insufficiency.	2.0 mm.	Normal	Splintering
24	54	m	+	Luetic aortic insufficiency.	5.8 mm.	Normal	T ₁ -T ₂ depressed
25	52	m	+	Luetic aortic insufficiency.	5.0 mm.	Normal	T ₁ -T ₂ inverted
26	34	m	++	Luetic aortic insufficiency.	4.0 mm.	Normal	T ₁ depressed splintering QRS
27	46	f	+++	Luetic aortic insufficiency.	5.5 mm.	Normal	Arborization block
28	63	m	+++	Luetic aortic insufficiency.	6.0 mm.	Normal	T ₂ -T ₃ inverted splintering
29	44	m	+	Luetic aortic insufficiency.	5.0 mm.	Normal	
30	36	m	++++	Luetic aortic insufficiency.	7.0 mm.	Normal	
31	39	m	+++	Mitral stenosis.	5.0 mm.	Fibrillation	T ₂ -T ₃ inverted
32	26	f	+	Mitral stenosis.	6.5 mm.	Normal	
33	25	m	+	Mitral stenosis.	4.5 mm.	Normal	
34	52	m	+	Nephrosclerosis.	4.0 mm.	Normal	Splintering
35	59	m	+++	Nephrosclerosis.	4.5 mm.	Normal	Splintering
36	71	m	+++	Nephrosclerosis.	3.0 mm.	Fibrillation	Splintering Coronary T
37	60	f	+	Nephrosclerosis.	5.0 mm.	Fibrillation	Splintering
38	56	f	+	Nephrosclerosis.	5.0 mm.	Fibrillation	Splintering

Group III is a miscellaneous group as far as the type of pathological findings is concerned. Acute and chronic infections of various types play the predominating rôle in this group. Of particular interest are the 2 cases of cancer which present no evidence of cardiac disease except such as may accompany cachexia. No doubt the anemia accompanying the malignant disease produced conditions in the cardiac conduction

system or myocardium which caused the low voltage to appear. This miscellaneous group, characterized by an absence of disease of the coronary arteries, comprises 12 cases (24 per cent) of the entire series of 50 cases. Table III illustrates in detail the cases of this type.

TABLE III
GROUP III. MISCELLANEOUS GROUP WITHOUT CORONARY DISEASE

CASE NO.	AGE	SEX	PATHOLOGICAL FINDINGS	MAX- IMUM VOLTAGE	MECH- ANISM	OTHER ELECTRO- CARDIOGRAPHIC FINDINGS
39	52	m	Mitral and aortic stenosis. Acute and chronic endocarditis.	4.5 mm.	Normal	
40	60	m	Cardiac hypertrophy and dilatation (chronic alcoholism).	5.0 mm.	Fibrillation	
41	31	m	Lobar pneumonia. Acute nephritis.	6.0 mm.		Slurring
42	52	m	Lobar pneumonia.	7.0 mm.	Normal	T ₁ -T ₂ depressed
43	66	m	Tuberculous pericarditis with effusion. Miliary tuberculosis.	7.0 mm.	Normal	T ₁ -T ₂ depressed
44	8	f	Subacute bacterial endocarditis.	3.0 mm.	Fibrillation	Splintering
45	30	f	Chronic and acute endocarditis. Adhesive pericarditis.	4.2 mm.	Normal	T ₁ -T ₂ -T ₃ isoelectric
46	46	f	Generalized arteriosclerosis. Sclerosis mitral valve. Tuberculous mediastinitis.	5.5 mm.	Normal	Arborization block
47	66	f	Generalized arteriosclerosis.	4.1 mm.	Fibrillation	T ₁ -T ₃ inverted
48	70	m	Brown atrophy of heart. Carcinoma of stomach.	5.5 mm.	Normal	
49	63	m	Carcinoma of stomach with hemorrhage.	4.5 mm.	Fibrillation	
50	59	m	Aortic insufficiency with perivascular infiltration about coronaries. Luetic.	6.0 mm.	Normal	Splintering

The maximum excursion of the QRS complex in any lead of the records studied is 7 mm. The lowest is 1 mm. The average measures 4.54 mm. The most common electrocardiographic abnormality aside from the low voltage is the splintering or slurring of the QRS complex which is found in 26 instances (52 per cent).

T-waves of the cove-plane type, so-called "coronary T-waves," appear in 2 cases (4 per cent). Arborization block is found in 3 instances (6 per cent).

Normal mechanism is present in 37 (74 per cent) of the cases. Nodal rhythm appears once, while fibrillation is present in 12 instances (24 per cent).

In 6 cases (12 per cent) right axis deviation is present. Left axis deviation is found in 20 cases (40 per cent). The remaining 24 cases (48 per cent) show no variation from the normal range.

The accompanying electrocardiograms are typical of the series in this study.

COMMENT

In reviewing the series of 50 cases as a whole, it is apparent that the most frequent pathological finding associated with the electrocardiogram of low voltage is coronary arteriosclerosis. Such sclerosis occurring either as a primary lesion or in association with some other cardiac abnormality, such as luetic or rheumatic heart disease, must interfere with the oxygenation of the conduction system sufficiently to reduce the electrical potential as measured by the electrocardiogram. The presence or absence of sclerosis of the coronary arteries will help to explain why in some instances of luetic aortic insufficiency we find records of high voltage, whereas in others the voltage is low, although in each instance the myocardial incompetency appears to be the same. The same

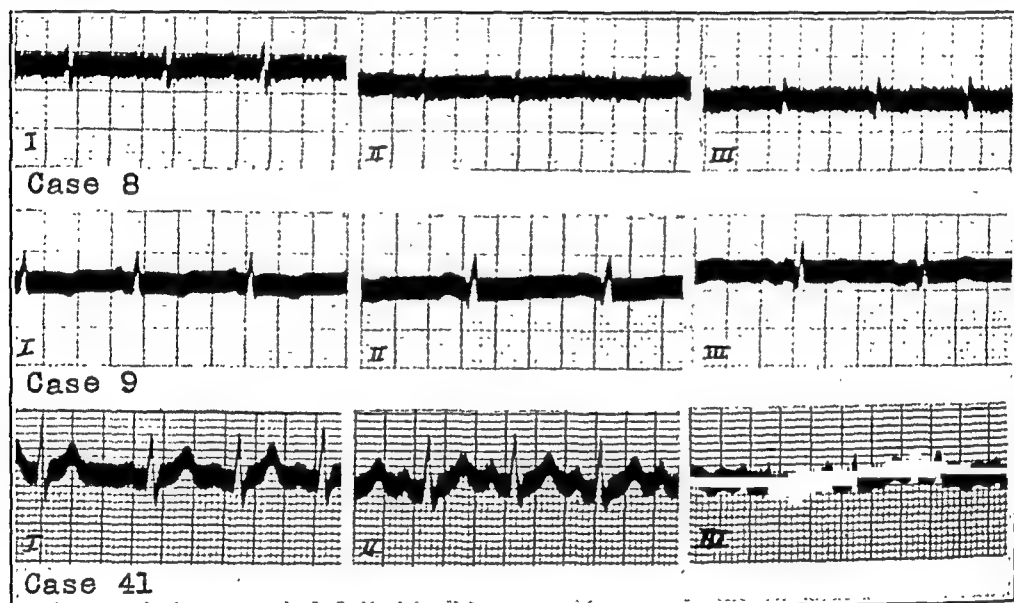


Fig. 1.—Typical electrocardiograms of low voltage.

set of circumstances may explain similar findings in cases of rheumatic heart disease.

In cases of acute or chronic infection or in cachexia (malignant disease) the problem is a different one. In these the toxic substance no doubt affects the conduction system directly and so alters the metabolic processes associated with the spread of the excitation wave through the Purkinje system.

SUMMARY

1. Fifty cases with electrocardiograms of low voltage are reported; all of these came to autopsy.

2. Coronary arteriosclerosis of significant degree was found in 76 per cent of these.

3. In the remaining 24 per cent acute or chronic infections play the most important rôle.

4. The low voltage electrocardiogram is most frequently associated with coronary arteriosclerosis in cases coming to autopsy.

Appreciation is expressed to the Department of Pathology of Cleveland City Hospital for the use of its records.

REFERENCES

1. Sprague, Howard B., and White, Paul D.: The Significance of Electrocardiograms of Low Voltage, *J. Clin. Investigation* 3: 109, 1926.
2. Speckman, Russel N., and Rich, Murry L.: Review of 50 Cases of Low Voltage, *J. Lab. & Clin. Med.* 17: 165, 1931.
3. Hepburn, J., and Jamieson, R. A.: Prognostic Significance of Several Electrocardiographic Abnormalities, *AM. HEART J.* 1: 623, 1925.
4. Pardee, Harold E.: *Clinical Aspects of the Electrocardiogram*, 1928, New York, Paul Hoeber.

Department of Clinical Reports

AN EARLY CASE OF CORONARY THROMBOSIS NOT HITHERTO REPORTED

HENRY F. STOLL, M.D.
HARTFORD, CONN.

THE development of coronary thrombosis during or following a hearty meal is of common occurrence. Though the pain is usually severe and sometimes referred to the epigastrium, it may be entirely lacking, the victim feeling only extreme weakness accompanied frequently by severe dyspnea.

Because vomiting is common, the condition until recent years was likely to be diagnosed as acute indigestion. Several factors probably contribute to cause an attack at this time. The coronary circulation, due to vessels already diseased, is definitely impaired though symptoms may have been lacking. As the stomach becomes distended, the position of the heart changes somewhat, and as a consequence the already impaired circulation may be further embarrassed. It may be also that the postprandial dilatation of the capillaries of the splanchnic system that accompanies digestion is associated with a diminution of blood flow in the coronary capillaries thus favoring thrombosis. Moreover the leucocytosis and platelet increase that accompany digestion possibly favor clotting.

If the assumption be correct that the patient in the case herein reported suffered from this condition, the case antedates considerably any hitherto reported.

CASE REPORT

G. B., aged eighty years, an itinerant teacher of philosophy, immediately after eating a hearty meal was seized with severe pain and great prostration and died a few hours later. The facts in the case are as follows:

A feast had been provided by the blacksmith of a small village. The menu was diversified and abundant. One dish was especially pleasing to the guest of honor, and he ordered that no one else should be served this particular food. There is some doubt as to just what this was but it seems probable that it consisted of pork. At any rate, after eating all he could, he evidently felt some discomfort, as he ordered that the remaining food be buried in a hole in the ground, remarking that no one else would be able to digest it. Almost immediately thereafter he was taken violently ill and suffered extreme pain. He is said to have passed some blood, probably from the bowels. He tried to conceal his suffering so as not to interfere with the festivity of the occasion and started forth on a journey on foot with some friends but very soon had to stop because of weakness and pain. He sat down on a blanket

and evidently suffered from shock as he complained bitterly of thirst, asking for water three times before it was possible to procure any. Feeling somewhat better, he proceeded on his way, but the increasing pain again forced him to stop, and this time he was evidently too weak to sit, as he lay down. It is stated that he lay on his right side. Inasmuch as one often sees individuals with serious cardiac disease who find that lying on the left side increases their pain, it is perhaps significant that he assumed the right lateral position.

With the great determination that had always characterized his life, he again attempted to proceed but was forced to lie down again; as formerly, he lay on his right side. The pain was obviously much less after he ceased the exertion of walking as he was able to converse with friends at considerable length. As his illness came on at once after dining, quite naturally some one suggested that it was due to something he had eaten. Accordingly, he sent for his host and publicly exonerated him for any responsibility in connection with his illness. This gracious act appears to have been nearer the truth than the generous sufferer may have suspected. He did not succumb until a number of hours after the onset of the attack.

Previous History.—He was the son of a very wealthy man. His mother died soon after his birth. He was evidently much pampered during his early childhood and at eighteen married his cousin. For ten years they lived the usual purposeless life of the idle rich. Becoming very much bored with the futility of this type of existence and being disappointed by his childless marriage, he finally deserted his wife and the baby which arrived too late to conquer his ennui. For six years he lived in the open, subsisting on a very poorly balanced and inadequate diet especially low in protein. It consisted chiefly of dry mosses, roots and wild fruits. As the result of this diet he became exceedingly emaciated. Later his manner of living and diet changed materially, but he was always temperate in his habits. In the main, his health appears to have been good.

Because of his catholic ideas, he often dined with individuals of widely different social stations. Thus we see him as the guest of honor at a feast given by certain wealthy nobles and shortly thereafter he was entertained at an even more elaborate affair, the hostess being a well-known courtesan. Not long after the latter dinner party he became very ill. The nature of this sickness is unknown, but it seems probable that it was some sort of an infection as he became much emaciated and his death was reported. He appears to have recovered by the time of the party given by the blacksmith but it may be that this infection predisposed him to coronary thrombosis as sometimes appears to be the case.

It is of interest further that he was of the square-shouldered or pyknic type, as such individuals are thought to be especially prone to occlusion of the coronary vessels.

The old gentleman whose final illness we have been considering died in the fifth century B.C. His name was Gotama Buddha.

REFERENCES

- Thomas, E. J.: *Life of Buddha; Its Legend and History*, 1927.
Encyclopaedia Britannica.
Saunders, K. I.: *Gotama Buddha*, Association Press, N. Y.

PARADOXICAL EMBOLISM OF THE CORONARY ARTERY*

MENDEL JACOBI, M.D., MAURICE KENLER, M.D., AND
IRVING SILVERMAN, M.D.
BROOKLYN, N. Y.

WHILE acute occlusion of the coronary arteries occasioned by endarterial changes and thrombosis or by spasm is a common clinical diagnosis, made daily and confirmed frequently at the section table, gross embolism of these vessels is apparently a very rare condition, receiving scant attention in works on cardiology or special pathology^{1, 2, 3, 4} and but little more in the periodicals.^{5, 6}

A recent comprehensive review of the literature by Saphir⁷ disclosed but eleven cases of true coronary embolism. These were associated with intrinsic cardiac or vascular disease. Still rarer are cases of paradoxical embolism of these vessels; the literature contains only the cases of Wolff and White,⁸ of Thompson and Evans⁹ (a case of tumor embolus) and the first of Saphir, and these were also associated with intrinsic cardiac or vascular pathology. Because of the rarity of the lesion, the sudden and unusual clinical course, and the complete absence of associated cardiac disease, the following case is being reported.

CASE REPORT

Mrs. M. R., aged forty-seven years, white, entered the medical service of Staten Island Hospital with the chief complaint of upper abdominal cramps of three days' duration.

Her family history and marital history were unimportant. She had had typhoid fever at twelve years, pneumonia at nineteen years, a two-stage thyroidectomy at thirty-four years, and a panhysterectomy at forty-four years.

Her present illness dates back to six days prior to entry when she developed vague aches and pains and was treated by her family physician for "grippe." A few days later she developed vomiting, diarrhea, and abdominal cramps. Except for slight dyspnea on exertion during the past three years, and an occasional attack of "dull ache" over the precordium, transient and related to excitement, the rest of the history was unimportant.

Physical examination on admission revealed a fairly well-developed but undernourished, white, middle-aged female, with an anxious expression and an appearance of exhaustion. Emotionally she was unstable. Temperature 98.6°, pulse 90 and respirations 20. Urine showed a slight trace of albumin and the blood showed a secondary anemia and a relative lymphocytosis.

Head, scalp, ears, nose, throat and lungs gave negative signs. On ophthalmoscopic examination there was recent hemorrhagic exudate on the temporal side of the right disc. There were two well-healed scars over the anterior aspect of the neck.

*From the Medical and Pathological Services of the Staten Island Hospital, and the office of Chief Medical Examiner, C. G. Norris, New York City.

Examination of the heart was not particularly remarkable. Apex beat was not seen or felt. No thrills. No enlargement. Sounds were regular and of good quality. Ventricular rate equalled pulse rate (100). Blood pressure was 100/75 mm.

The admission diagnosis was gastroenteritis, and she was given a low residue diet, bismuth salts and sedatives. Within a few days there was a decided improvement. It is perhaps worthy of mention here that she had no symptoms referable to the cardiorespiratory system during the course of her stay in the hospital.

On the sixth day of her stay in the hospital, while lying flat on her back she was suddenly seized with a sharp, agonizing substernal pain. Within fifteen minutes she was pronounced dead.

Autopsy performed two hours after death disclosed a well-developed and fairly well-nourished middle-aged white female showing healed thyroidectomy and trans-



Fig. 1.—Heart opened and showing the embolus in left coronary artery (A), and the patent foramen ovale, with probe inserted (B).

verse lower abdominal operative scars. The face, oral mucosae, finger and toe nails were markedly cyanotic, the remainder of the skin was somewhat less cyanotic. There was no rigor or post-mortem discoloration in any portion of the body; the entire body was quite warm. There was a slight but definite pitting edema of the entire left lower extremity, most marked over the ankle but present also over the buttock. There was no edema in any other portion, and there were no evidences of varicose veins in either extremity.

On opening the thoracic cavity, several complete auricular contractions were observed, tapering off into fibrillary twitches of the left ventricle, while the lungs rapidly deepened in red color and the abdominal veins and pulmonary artery became visibly distended with venous blood. The heart itself weighed 300 gm.; the endocardium, pericardium and valves were all smooth, glistening and translucent throughout; the myocardium was of good tone; all somewhat paler than usual. The foramen

ovale presented an opening 0.5 cm. in diameter. In the anterior descending branch of the left coronary artery was a soft, lamellated gray red thrombus, 1 cm. in length and 0.3 cm. in diameter, which completely plugged the vessel from a point just beyond its origin distalward for about 0.6 cm., the embolus being curled on itself; there was no propagated or retrograde thrombus. The plug was very easily removed from the vessel, disclosing the underlying intima smooth, glistening, and utterly devoid of atheromatous change. A similarly smooth and glistening intima was present in the other coronary branches. The aorta presented a few pinhead sized soft yellowish atheromatous patches in the intima of the arch, everywhere, however, covered by smooth and glistening surfaces. In fact the entire aorta and its branches were surprisingly free of atherosclerotic changes. No aortic valvular, commissural, or coronary orificial changes suggestive of syphilis were present. No thrombi were present in either auricular appendage. There were no vascular anomalies except for the patent foramen ovale.

The lungs were well aerated, not edematous, but congested. Their entire vascular tree, arterial and venous, showed no intrinsic or thrombotic changes. The abdominal viscera were moderately congested. In the left kidney a recent white infarct a few millimeters in diameter was present on the midanterior surface. The uterus, left tube and ovary and right tube were absent; the right ovary was firm and contained several corpora lutea of varying size and a few retention cysts. The entire vaginal vault was covered by old peritoneal adhesions.

The left femoral vein was thickened. Just distal to its entrance into the iliac vein, it was partially occluded by firm brownish red tissue, to the proximal end of which a grayish red, softer thrombus, similar grossly to that found in the coronary artery, was still attached. The intima under both types of thrombus was dulled and roughened when the latter was detached. The remaining pelvic and abdominal veins, and the right femoral, thoracic, and cervical veins were unchanged.

Sections of the embolus in the coronary artery and similar fragments in the femoral vein were composed of lamellated platelet-erythrocyte thrombus with some admixture of polymorphonuclear leucocytes. Sections of the firmer brown red femoral thrombus consisted of partially canalized hyalinized fibrous tissue which merged, without demarcation, with the venous wall. The latter showed elastica fragments in the contact zone but no definite elastica. The media was fibrosed but not cell-infiltrated; the adventitia was unaltered.

Sections of the kidney through the infarcted area disclosed the usual picture of a bland infarct. The remainder of the kidneys, as well as the lungs and abdominal viscera, presented the picture of an acute passive congestion.

Sections of the heart through interventricular septum and adjoining portions of the ventricles showed the cytoplasm and nuclei swollen and poorly stained. Elsewhere there were no cellular changes and no evidence of recent or old rheumatic, syphilitic, or arteriosclerotic vascular changes.

DISCUSSION

The possibility of embolism in this case was entirely overlooked clinically because of the apparent absence of a source. The precordial pain and the dyspnea, not typically anginoid in character, might have suggested cardiovascular occlusive changes, particularly in the absence of any evidences of hypertension or organic vascular disease. Had the buttock and ankle edema of the left lower extremity present at the autopsy table been noted ante-mortem, it might have given a suggestive lead to a potential source of embolism.

Of interest was the continued cardiac contraction after clinical death and at the autopsy and the visible termination in ventricular fibrillation, both findings not of frequent record. The case is of further interest in that it is the only one on record in which a long antecedent and already organized venous thrombosis has given rise to coronary embolism. In other respects, such as the branch involved and the mode of death, it corresponds to the general findings in Saphir's review. No such factors as depletion of the pulmonary circulation, or significant differences in the caliber between the aortic and coronary orifices were present in this case to explain the coronary involvement, as suggested in Saphir's review. In view of the embolic phenomena in other organs, we feel that the coronary involvement was purely incidental to a general embolizing process.

SUMMARY

A case of acute coronary occlusion due to an embolus from an old thrombosis of the femoral vein in the presence of a patent foramen ovale is reported. There were no associated arterial or endocardial changes. The factors in its production are discussed briefly.

REFERENCES

1. Sutton, D. C., and Lueth, H.: *Diseases of the Coronary Arteries*, St. Louis, page 98, 1932, The C. V. Mosby Co.
2. Jores, L.: in Henke-Lubarsch *Handbuch der Allgemeine Pathologie u. Pathologische Anatomie*, Bd. 11, Berlin, p. 622, 1924, J. Springer.
3. Welch, W. H.: in *Albutt System of Medicine*. Vol. VI, New York, p. 281, 1900, The Macmillan Co.
4. Kaufman, E.: *Special Pathologic Anatomy*, Translated by Reimann, S., Vol. I, p. 56, Philadelphia, 1930, J. B. Lippincott & Co.
5. Benson, R. L.: *Arch. Path.* 2: 876, 1926.
Gallavardin, L., and Dufourt: *Lyon med.* 121: 141, 1913.
Stevens, J. L.: *Tr. Glasg. Path. & Clin. Soc.* 10: 45, 1903-04.
6. Levy, Robert L.: *AM. HEART J.* 7: 431, 1932.
7. Saphir, O.: *AM. HEART J.* 8: 312, 1933.
8. Wolff, L., and White, P. D.: *Boston M. & S. J.* 195: 13, 1926.
9. Thompson, T., and Evans, W.: *Quart. J. Med.* 23: 135, 1930.

Leroy Crummer

APRIL 15, 1872—JANUARY 2, 1934

THE recent lamented death of Doctor Crummer removes a nationally known and greatly respected figure in the fields of internal medicine and medical history.

After being graduated from the Northwestern University Medical School in 1896, Doctor Crummer lived most of his professional life in Omaha, where ultimately he became professor of medicine in the University of Nebraska College of Medicine (1919-1925).

During the War his services were requisitioned by the Army, and he rendered notable service as a teacher of physical diagnosis in the school for civilian medical officers established at Camp Greenleaf, Tenn.

His professional interests were especially keen in the field of heart diseases, and the popularity of his modest volume, *Clinical Features of Heart Disease*, attests his soundness as a clinician and teacher.

During the last few years of his life, an invalid himself from heart disease, Doctor Crummer resided in Los Angeles and devoted himself almost entirely to his fine library and to studies in medical history. His distinction in this field was recognized at both the University of California and the University of Southern California by his appointment to a professorship in medical history.

As an honored member of the Advisory Editorial Board of the AMERICAN HEART JOURNAL his loss is deeply felt.

Department of Reviews and Abstracts

Book Review

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG VI
TAGUNG. Edited by Dr. Bruno Kisch. Theodor Steinkopff, Dresden and Leipzig,
1933, 276 pages.

The sixth annual meeting of the Deutsche Gesellschaft für Kreislaufforschung was given over to a discussion of the relation between the circulatory and nervous systems. The first part of the program is experimental, the second clinical in view-point; both parts contain interesting and instructive papers.

E. H.

STROPHANTHIN-THERAPIE. By Professor Dr. A. Fraenkel, Heidelberg, with the collaboration of Dr. R. Thauer, Frankfort, Berlin, Julius Springer, 1933, 148 pp.

The introduction affords an accurate guide to what one may anticipate in the author's treatment of the subject, in that he declares his preference for the treatment of cardiac insufficiency by means of the intravenous injection of strophanthin. The table of contents permits one to turn at once to any particular phase of this subject—history, botany, pharmacognosy, chemistry, pharmacology, or therapy—in which one may be especially interested. Each division is followed by references to the literature arranged alphabetically. The several bibliographies include references to more than 750 papers. The monograph itself being mainly a review of the essential literature, the present reviewer finds it difficult to give anything approaching a satisfactory review of it without exceeding the space permitted.

Some thirty-five pages are devoted to the division entitled, "The Pharmacology of Strophanthin." This division in reality is devoted mainly to the pharmacology of digitalis, but, as the author states, the actions of digitalis and strophanthin are qualitatively similar after they have entered the blood stream. The author has shown discernment in the selection of papers which he has reviewed, but, naturally, no monograph of this size can fail to omit reference to some papers that may be considered important. The author refers repeatedly to the work of Weese, who compared the amounts of digitoxin and strophanthin taken up by the heart with those fixed in other organs, and since he bases important conclusions on this work, it may be proper to state that reference to Weese's paper shows that his results do not uniformly substantiate his conclusions. The discussion of the toxic side actions of the digitalis bodies is confined almost exclusively to that of nausea and vomiting. The biological standardization of the digitalis bodies is discussed concisely, but the author considers it of value only as showing the degree of constancy of activity of a given preparation. That view is tenable for one who administers digitalis bodies orally, much more than in the case of one who injects them intravenously; in the latter case the actual activity of different substances is more nearly proportional to the indicated activity than when they are administered orally. More than half of the monograph (about eighty pages) is devoted to the clinical use of the digitalis bodies, with arguments in favor of the intravenous use of strophanthin. This is

presented systematically and includes the history of intravenous therapy, the technic, the observation of the use of strophanthin in practice, indications and dosage, with numerous case histories, tracings, electrocardiograms and x-ray photographs of the heart.

The author is obviously impressed with the superiority of strophanthin over other substances designed for intravenous injection, but when he states that one of the advantages of strophanthin is its relative nontoxicity ("relativen Ungiftigkeit"), one wonders just what is meant, because it is very well known that the fatal dose of a digitalis body closely parallels its therapeutic activity. If by "Ungiftigkeit" the author means its relatively slight nauseant and emetic action, it is at least understandable, because strophanthin is relatively less nauseant than some of the proprietary preparations with which the author compares it; but this statement must not be understood as indicating that it is less dangerously toxic. In pointing out the advantages of strophanthin over nearly similar substances, the argument is occasionally strained (page 77).

When one has read the monograph carefully, one is impressed with the difficulties of treating cardiac disease wisely without that mastery of the subject which can be acquired only by long, patient, painstaking observations of symptoms and of the varying effects of the therapeutic use of digitalis. In this country, at least, it is the nearly unanimous opinion of cardiologists that the oral administration of digitalis suffices for the treatment of nearly all patients with cardiac disease who are capable of responding to it with any form of administration, and it must be apparent to all that the intravenous injection of strophanthin is dangerous in the hands of any but the well-informed cardiologist, though it is beyond question that nearly every physician will occasionally see a patient suffering with acute cardiac failure who needs an intramuscular or intravenous injection of one of the digitalis bodies.

A word of praise is due the publisher. This monograph is beautifully printed and the illustrations and tracings show exquisite workmanship, so that it is a pleasure to read it.

R. A. H.

The American Heart Journal

VOL. 9

APRIL, 1934

No. 4

Original Communications

SYPHILITIC DISEASE OF THE CORONARY ARTERIES*†

HOWARD G. BRUENN, M.D.
NEW YORK, N. Y.

INTRODUCTION

AN ABUNDANT literature has appeared in recent years dealing with various aspects of cardiovascular syphilis. Relatively little, however, has been recorded concerning syphilitic disease of the coronary arteries, and a satisfactory correlation between the clinical and pathological features has not been established. It is the purpose of this paper to define the rôle of this affection in relation to the general picture of syphilis of the heart and aorta.

Anatomically, syphilitic disease of the coronary arteries manifests itself in two ways: (1) obstruction to the coronary blood flow by stenosis or occlusion of the orifices of the coronary arteries, and (2) syphilitic involvement of the branches distal to the orifices. The rôle of syphilis in producing lesions of the latter type is of questionable importance. Warthin,¹ who maintained that localized syphilis of the smallest arterioles is an essential part of the general pathological condition of chronic or latent syphilis, added that "syphilis of the coronary arteries, in our experience, has been found much less frequently than anticipated from its frequent mention in the literature. . . . the larger branches of the coronaries only rarely show lesions that can be recognized as syphilitic." Maher² described changes of the larger branches of the coronary arteries similar to those found in the aorta. Moritz³ recently reported cases with like findings in those portions of the coronary arteries just outside the aorta. On the other hand, Martland,⁴ Clawson and Bell,⁵ Leary and Wearn,⁶ and Coombs⁷ concluded that syphilitic coronary disease, except for involvement of the orifices, was rare. Scott⁸ stated that "it is interest-

*Submitted in partial fulfillment of the requirements for the degree of Master of Science in the Faculty of Medicine, Columbia University.

†From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital.

ing to note that in spite of the active disease surrounding their orifices, the coronary vessels themselves were seldom involved."

The study of our material has indicated that syphilis of the coronary arteries distal to their orifices is an uncommon lesion and is rarely of clinical importance. This paper will, therefore, concern itself only with syphilitic stenosis or occlusion of the coronary orifices.

While the involvement of the aorta by syphilis was first suspected by Paré⁹ and Morgagni,¹⁰ the significance of this process in occluding the coronary arteries at their orifices has only recently been stressed. The first observations appeared about the latter part of the nineteenth century and were in the form of pathological reports, such as those quoted by Allbutt¹¹ and O'Sullivan.¹² Further interest in this type of coronary involvement was stimulated by the two cases reported by Cannon¹³ in 1929, and more particularly, by the paper of Leary and Wearn⁶ published in the same year.

MATERIAL*

The material on which this study is based includes all of the cases of syphilitic cardiovascular disease which came to autopsy in the Presbyterian Hospital between the years 1910 and 1932, inclusive. During this period, 3,190 autopsies were performed of which 148 showed syphilitic involvement of the heart and aorta, an incidence of 4.6 per cent. The figure approximates those reported by other writers.

TABLE I
INCIDENCE OF CARDIOVASCULAR SYPHILIS AT AUTOPSY

AUTHOR	LOCALITY	NO. OF AUTOP-SIES	NO. OF CASES WITH CARDIOVAS-CULAR SYPHILIS	PER CENT
Symmers ¹⁵	New York	4,880	175	3.5
Reid ¹⁶	Boston	1,678	54	3.2
Cowan and Faulds ¹⁷	Glasgow	1,000	60	6.0
Cullinan ¹⁸	London	1,000	33	3.3

The degree of narrowing of the coronary orifices was variable. There were only 8 cases in the entire group of 148 which showed extreme stenosis or complete occlusion of the right or the left coronary openings. There was a considerable number, however, with a sufficient degree of stenosis to have produced serious embarrassment to the coronary blood flow during life. Clawson and Bell⁵ in a similar group of cases published in 1927 give approximate values for the extent of the narrowing expressed in terms of fractions of the normal, but make no mention of a method of measurement. Moritz³ and Saphir and Scott,¹⁹ in their series of cases, describe the extent of the narrowing merely as "some stenosis" of the coronary orifices.

*Part of this material has already been studied from another viewpoint by Lamb, Turner, Golden and Von Glahn.¹⁴ The discrepancies between their figures and the following are accounted for by the longer time period covered in the present series of observations.

The size of a normal coronary orifice has not been clearly defined. In the absence of a normal standard for comparison it is impossible to recognize the lesser degrees of narrowing or to estimate the degree of stenosis. By means of a small, cone-shaped piece of steel, the circumference of which was calibrated in millimeters, it was possible to measure with a fair degree of accuracy the orifices of the coronary arteries in terms of their circumferences. From the inner surface of the aorta, this instrument was inserted as far as possible into the mouths of the coronary arteries. Care was taken that the tip should not be obstructed within the vessel itself, and just enough pressure was exerted to have the instrument fit snugly into the opening. The measurement of the orifice was read from the calibrations on the instrument. Fortunately, 118 hearts of the 148 cases of cardiovascular syphilis had been preserved, and these specimens were measured as described.

In addition, 25 nonsyphilitic cases of similar age groups were selected as a control series, these cases presenting varying pictures of disease, different weights of hearts, with and without arteriosclerosis of the aorta, but with no obstruction to the mouths of the coronary arteries. In measuring this control group, it was found that the average coronary artery orifice measured about 10 mm. in circumference. The normal range was from 8 to 11 mm.

TABLE II
MEASUREMENTS OF CORONARY ORIFICES IN 118 CASES OF AORTIC SYPHILIS

	NO. CASES WITH NORMAL ORIFICES	PER CENT	NO. CASES WITH MARKED STENOSIS	PER CENT
Simple aortitis	40	50.6	4	10.3
Aortitis with aortic valve involvement	18	22.8	25	64.1
Aortitis with aortic valve involvement with aneurysm	10	12.6	9	23.0
Aortitis with aneurysm	11	14.0	1	2.6
Totals	79	100	39	100

Carr,²⁰ in a group of 119 cases of cardiovascular syphilis, found coronary orifice involvement in 10 (8.4 per cent). Clawson and Bell⁵ reported 25 cases of sudden death from closure of the coronaries in a series of 126 cases, an incidence of 19.8 per cent. In Martland's⁴ group of 101 cases, the coronaries were involved in 15 (14.9 per cent). In the series studied by Saphir and Scott,¹⁵ 37 out of 107 cases of luetic aortitis (35 per cent) were found to have narrowed coronary orifices.

In the present series of 118 hearts, 42 (35.6 per cent) showed patent coronary orifices measuring over 10 mm. in circumference; in 37 cases (31.4 per cent) one or both openings ranged between 8 and 10 mm.;

while 39 cases (33.0 per cent) had coronary orifices one or both of which measured 7 mm. or less in circumference. This gives a total normal group of 79 cases (66.9 per cent.) and 39 cases (33.1 per cent) with stenosed orifices.

This table shows a significant yet obviously logical fact. Syphilis involving the aortic valve is often accompanied by narrowing of the coronary orifices. Of the 39 cases showing definite stenosis to complete occlusion, 34, or 87.1 per cent, also showed involvement of the aortic valves by the luetic process. This frequent association of aortic insufficiency with coronary orifice involvement has been commented upon by most authors. Furthermore, of the 5 cases showing stenosis of the coronary orifices but with no aortic regurgitation, 4 patients never complained of any cardiac symptoms and died of various affections, quite unrelated to heart disease (cirrhosis of the liver, carcinoma, brain tumor and paralytic ileus). Thus, a consideration of syphilitic coronary orifice involvement resolves itself into a discussion of aortic insufficiency with and without this complication.

PATHOLOGY

In most of the forms of obliterative endarteritis of vessels of the size of the coronaries, occlusion depends upon the formation of a thrombus which subsequently undergoes organization. For example, accompanying and following senile involution of the uterus and ovaries, an active endarteritis usually occurs but thrombosis is often a factor in leading to occlusion of the vessel. In thromboangiitis obliterans, as well as in syphilitic disease of the cerebral vessels, thrombosis is the usual process by which the lumen of the vessel is closed. On the other hand, closure of the coronary arteries due to syphilis is always caused by encroachment on the orifices of the arteries by supravulvular sclerosis of luetic origin.

Microscopically, the process is similar to that seen in other portions of the aorta. There occurs an obliterative endarteritis of those vasa vasorum which penetrate the muscular coat of the coronary arteries. The consequent impairment of blood supply leads to nutritional disturbances which are localized to those portions of the coronary vessels which lie within the aortic wall. A progressive increase of the subendothelial layer of the coronary intima takes place which narrows the lumen of the vessel until total occlusion may result. The process preserves intact the endothelial lining of the coronary lumen, so that thrombosis does not occur.

In these cases, interference with efficiency of the coronary blood flow becomes marked. The process of occlusion is very gradual, however, and a collateral circulation may be set up, in part, perhaps, through the Thebesian vessels.²¹ The fact that the closure progresses slowly explains the comparative immunity of the patient from symp-

toms and the remarkable freedom of the myocardium from scarring, although the coronary circulation is impaired.

In a series of 20 cases, Clawson and Bell⁵ noted 4 in which there was complete closure of coronary orifices—4 of the right, none of the left. Reid²² reported 5 similar cases—3 of the right, one of the left, both in one. Cannon's¹² two cases showed occlusion of the left in one case, of the right in the other. In the two cases reported by Leary and Wearn⁶ the right coronary orifice was occluded in both, the left in one. Of the 39 cases of this series in which stenosis of the coronary orifices was present (the circumference being 7 mm. or less) the right coronary artery was involved in 9 cases, the left in 4, and both orifices were affected in 26 cases. If only total occlusion is considered, the right coronary orifice was obliterated in 8 cases, the left in one. A compilation of these statistics, including the present series, leaves the right occluded in 19 cases, the left in 5. There is no apparent explanation at the present time for the greater frequency and severity of right coronary orifice involvement.

As the syphilitic process usually stops at the upper level of the sinus of Valsalva except for penetration along the attachments of the valves, an abnormally high origin of the coronary arteries might well be an important factor in the involvement of their orifices. That this inference is borne out by the facts was first pointed out by Von Glahn²³ in 1923, and is shown in Table III.

TABLE III

POSITION OF THE CORONARY ORIFICES IN RELATION TO THE UPPER LEVEL OF THE SINUS OF VALSALVA*

	ABOVE		AT		BELOW	
	L.	R.	L.	R.	L.	R.
Coronary orifices patent (42 cases) over 1 cm.	3	6	6	4	14	12
Slight stenosis (37 cases) 8-10 mm.	15	10	3	2	13	17
Marked stenosis (39 cases) 7 mm. or less	17	13	3	4	3	4

*These cases include in part those reported by Von Glahn²³ in 1923, as well as those in his later publication.¹⁴

The most conspicuous anatomical change noted in the myocardium with aortic insufficiency is cardiac hypertrophy, especially of the left ventricle. The average increase in weight of the heart is fully as great as that found in cardiac failure associated with hypertension. This hypertrophy appears to be the result of aortic regurgitation. The smallest and largest heart in the group with stenosed orifices and in that with normal orifices weighed about the same, respectively 250 and 1,100 gm., yet as seen in Table IV, on the average the hearts with stenosed coronary orifices were less heavy.

TABLE IV

STATE OF THE MYOCARDIUM IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

	NORMAL CORONARY ORIFICES (28 CASES)	STENOSSED CORONARY ORIFICES (34 CASES)
Aortic ring	7.72 cm.	7.75 cm.
Weight of heart	711 gm.	577 gm.
Gross myocardial fibrosis		
none	20	21
slight	4	4
moderate	2	1
marked	1	1
infarction	1	2

It is conceivable that interference with the blood flow through the coronary arteries diminishes the ability of the heart to enlarge. Arteriosclerosis of the coronary arteries was approximately of the same frequency in both groups. Aschoff bodies in the myocardium were found in 3 cases of the group with normal orifices, in one case with stenosed coronary orifices. Hypertension was no more frequent in one group than in the other. It will be shown that no great variation exists in the average of the two groups as regards time of onset of infection and duration of life.

Gross areas of myocardial fibrosis occurred with approximately the same frequency and were of about the same degree of severity in each group. There was, in general, sufficient atheromatous change in the arteries themselves to account for the amount of fibrosis present. Certainly, no correlation was apparent in the group with stenotic orifices between the degree of stenosis and the amount of scarring. However, in most cases showing marked stenosis or complete occlusion of the coronary orifices, there was little or no fibrosis either grossly or microscopically. Infarction of the heart in this condition is a relatively rare complication, there being only 3 instances of infarction in this series in which the scarring was due to stenotic coronary orifices. Saphir²⁴ has reported a similar case of infarction.

CLINICAL FEATURES

The part played by the narrowing or occlusion of the coronary orifices in coloring the clinical picture of luetic aortitis has been subject to much conjecture. There exist no clear-cut criteria at the present time which enable the clinician to make a positive diagnosis. To determine if there were differences in the manifestations of cases of aortic regurgitation with and without stenosis of the coronary openings, the clinical data were compared.

A comparison of these two groups of cases shows that there was a slightly lower age level in the group with stenosed coronary orifices, as indicated in Table V.

TABLE V

RACE, AGE, SEX AND DURATION OF LIFE IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

		NORMAL CORONARY ORIFICES (28 CASES)	STENOSED CORONARY ORIFICES (34 CASES)
Race	Negro	7	16
	White	20	17
	Yellow	1	1
Sex	Male	23	27
	Female	5	7
Age at time of initial lesion		25.3 yr. (18-38)	23.6 yr. (14-32)
Age at time of cardiac symp.		51.2 yr. (32-69)	46.3 yr. (25-62)
Duration of latent period		22.7 yr. (4-35)	20.5 yr. (5-39)
Time from first cardiac symptom to admission		8.75 mo. (1 wk.-3 yr.)	8.2 mo. (1 wk.-3 yr.)
Time from first cardiac symptom to death		11.4 mo. (1 wk.-3 yr.)	9.9 mo. (2 wk.-3 yr.)
Duration of life from primary lesion		23.4 yr. (4-35)	21.1 yr. (5-39)

The tendency of the colored race to develop cardiovascular syphilis is well known. Not only is the incidence of cardiovascular syphilis high in the negro, but the average age at which he first develops cardiac symptoms is much lower than that for the white. Whether this fact is due to the earlier age at which the negro is infected, or whether it is due to the more rapid and virulent course which the infection runs in this race must remain in doubt, as there were not sufficient data on the latent period of the infection. The ratio of whites to negroes in the total autopsy series in this hospital is about 11:1. In the cases of cardiovascular syphilis, the ratio becomes reduced to 3:1. In the cases of syphilitic involvement of the coronary openings the ratio of negroes to whites is further reduced to 1:1. In other words, approximately 50 per cent of the negroes in the entire series of cardiovascular syphilis (18 out of 37 cases) had partially or completely occluded coronary orifices, as compared to 21.5 per cent of the whites (17 out of 79 cases). This fact may be of some importance in explaining the severity of syphilitic cardiovascular disease in the negro.

TABLE VI

CLASSIFICATION OF CHIEF COMPLAINTS IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

	NORMAL CORONARY ORIFICES (28 CASES)	STENOSED CORONARY ORIFICES (34 CASES)
Dyspnea	18	20
Orthopnea	2	4
Paroxysmal nocturnal dyspnea	3	0
Pain (cardiac)	10	13
Edema	5	7
Cough	4	3
Weakness	2	6
Insomnia	1	0
No cardiac symptoms	2	4

Chief Complaints.—The chief complaints which brought the patient to the hospital are shown in Table VI. Dyspnea and cardiac pain were much the most common. As can be seen, however, no striking differences exist between the two groups.

TABLE VII

CLASSIFICATION OF SYMPTOMS IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY*

	NORMAL CORONARY ORIFICES (28 CASES)	STENOSED CORONARY ORIFICES (34 CASES)
Dyspnea	26	28
Orthopnea	16	21
Paroxysmal nocturnal dyspnea	9	14
Pain	19	26
Edema	14	11
Cough	17	16
Palpitation	10	12
Weakness	9	10
Choking	2	4
Insomnia	11	9
Hoarseness	3	1

*Two of the cases with normally patent coronary orifices and four of the cases with stenosed orifices presented no cardiac symptoms.

TABLE VIII

CLASSIFICATION OF CARDIAC PAIN IN 40 CASES OF AORTIC INSUFFICIENCY*

	NORMAL CORONARY ORIFICES (16 CASES)	STENOSED CORONARY ORIFICES (24 CASES)
Type—		
Pain (severe, sharp, sticking, etc.)	6	13
Ache (distress, dull, soreness)	2	3
Oppression (squeezing, pressing, smothering)	2	5
Boring	0	1
Location—		
Precordium	5	6
Substernum	5	8
Epigastrium	3	9
Chest	0	0
Radiation—		
l. arm	2	8
r. arm		4
l. shoulder	1	4
r. shoulder		3
neck	0	1
back		3
substernum		3
precordium	1	1
abdomen		1
l. chest	1	
no radiation	1	4
Steady		
Attacks		

*In order to eliminate all cases with pain which might possibly be due to aneurysm, this table includes only cases of uncomplicated syphilitic aortic insufficiency. There were nine cases of aneurysm in the stenosed group and 10 in the group with normal orifices. Furthermore, 2 cases of aortic insufficiency in the normal and 1 case in the stenosed group were not included because of significant arteriosclerosis of the coronary arteries.

When these groups are compared as to total symptoms, there is again great similarity between them (Table VII).

Only minor variations in the frequency of the symptoms occurred. It should be noted with regard to pain that there was the same number of cases with aneurysm in the two groups. The frequency with which cardiac pain is experienced in aortic syphilis has been assumed by Coombs,⁷ among others, to be due to obstruction of the coronary orifices.

The clinical charts were incomplete in detail, especially in the earlier years, with respect to the description of cardiac pain. It does appear, however, that pain referred to the epigastrium is twice as common in those cases with coronary orifice occlusion as in the nonaffected group. In those cases with coronary orifice occlusion the pain has a definitely greater tendency to radiate than in the other groups. It is also of interest that cardiac pain was present in 15 cases (62.5 per cent) of the stenosed group in contrast to only 5 cases (27.8 per cent) in the other group. The absence of pain, however, does not rule out the presence of stenosis or occlusion. On the basis of the available data, clinical differentiation between the cases with involvement of the coronary orifices and those without such involvement is often difficult or impossible (Table VIII).

Physical Findings.—A consideration of the chief findings on physical examination is found in Table IX.

TABLE IX
CHANGES ON PHYSICAL EXAMINATION IN 59 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

	NORMAL CORONARY ORIFICES (26 CASES)	STENOSED CORONARY ORIFICES (33 CASES)
Cardiac hypertrophy—		
no enlargement	2	1
slight enlargement	9	18
marked enlargement	15	14
Rhythm—		
regular	17	22
extrasystoles	7	10
Gallop	4	5
Thrill	4	6
Peripheral sclerosis—		
none	2	3
slight	12	19
marked	4	1
Edema—		
none	4	12
slight	15	12
marked	4	7
Hypertension (over 160 systolic or 100 diastolic)	12	11

In addition to these, both groups showed some or all of the well-recognized signs of aortic insufficiency. Practically all the cases in each group showed a Corrigan pulse with a large pulse pressure, as well as the characteristic diastolic murmur. The hearts in the group with normal coronary orifices were usually markedly enlarged, while in the other group they tended to be only slightly enlarged. This finding on physical examination checks with the pathological findings. There was great similarity in the types of heart rhythm between the two groups. There was a slight tendency of the cases with normal coronary openings to show marked peripheral sclerosis, which may possibly be due to the somewhat greater age of these patients. The frequency of hypertension was approximately the same in both groups. Noteworthy, however, is the fact that over twice as many patients with stenosed coronary orifices failed to show edema as did those in the other group.

Roentgen Ray Examination.—No specific change in the x-ray picture can be attributed to syphilitic disease of the coronary orifices. The hearts are smaller in the group with stenotic orifices, but this difference in size is of doubtful diagnostic aid.

Wassermann Reaction.—Table X gives the results of the Wassermann reactions in the two groups. There are no conspicuous differences between them.

TABLE X
SEROLOGY IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

	NORMAL CORONARY ORIFICES (28 CASES)	STENOSED CORONARY ORIFICES (34 CASES)
Blood Wassermann—		
Strongly positive	25	27
Weakly positive		2
Anticomplementary		1
Negative	2	1
Test not performed	1	3
Spinal fluid—		
Strongly positive	1	4
Negative	2	4

Electrocardiogram.—The electrocardiogram in syphilitic aortitis shows no abnormalities which can be termed characteristic. The commonest finding is left axis deviation, which may well be associated with the hypertrophy of the left ventricle occurring with aortic insufficiency. Juster and Pardee²⁵ found abnormal T-waves in 85 per cent of 34 cases of aortic insufficiency. They state that "coronary narrowing by luetic aortic aortitis must lead to a defective nutrition of the heart muscle and this we believe is the cause of the abnormalities found in the electrocardiograms of our patient with aortic insufficiency." This opinion is not uncommon.

Electrocardiographic tracings were made in 13 cases with normal or slightly narrowed coronaries and on 12 cases which showed markedly stenosed or occluded coronary orifices (Table XI).

TABLE XI

ELECTROCARDIOGRAPHIC CHANGES IN 25 CASES OF SYPHILITIC AORTIC INSUFFICIENCY*

	NORMAL CORONARY ORIFICES (13 CASES)	STENOSED CORONARY ORIFICES (12 CASES)
Premature beats	3	4
Prolonged A-V conduction	3	2
Right axis deviation	0	1
Left axis deviation	11	8
QRS—		
abnormal duration	3	2
notched or slurred	7	7
low voltage	1	1
Total significant QRS abnormalities	11	10
T-wave—		
down in Lead I	3	5
down in Lead II	1	0
down in Leads I and II	5	4
diphasic in Lead I	1	0
low voltage	3	1
Total significant T-wave abnormalities	13	10
No abnormalities of T-wave	1	3
Bundle-branch block	3	4
Partial heart-block	1	0

*All cases with significant arteriosclerosis of the coronary arteries have been omitted from this table.

No significant differences between the two groups were found. The abnormalities of the T-waves and of the QRS group as well as the frequency of occurrence of left axis deviation were approximately the same in both groups. It appears that abnormalities in electrocardiograms of patients with luetic aortic regurgitation cannot be ascribed solely to coronary orifice stenosis or occlusion.

Clinical Types.—A critical study of the cases with stenosed coronary orifices leads to the impression that one type of case stands out sharply by reason of certain distinctive features. There were 5 such cases in this series (14.7 per cent). They can be segregated roughly by age, but more definitely by the clinical and pathological findings.

1. They were characterized by their youth. All were in the third and fourth decades of life. No case in this series was alive after the age of forty years. The youngest was twenty-one years, the oldest thirty-nine. The average age was 33.6 years.

2. Sex and race were not distinctive.

3. Examination of the hearts showed little or no hypertrophy in the 5 cases of this series. The largest heart weighed 420 gm., the smallest 260 gm. The average weight was 370 gm.

4. Except in one instance, in which large atrophic scars were found, the myocardium was free of gross fibrosis. Histologically, there was a small amount of fine scarring, and two cases showed focal necroses.

5. In no instance was arteriosclerosis of the coronary arteries present. Both coronary orifices were extremely stenosed in 4 cases. The fifth case showed marked stenosis of the left opening and slight narrowing of the right. The right coronary orifice was occluded in two.

6. Pain was the predominant complaint in all. It was paroxysmal in type, being referred in one case to the precordium, in the others to the epigastrium or to the sternum. Radiation of the pain was present in 4 of the 5 cases.

7. The absence of edema in all cases was striking.

8. The average duration of life after the onset of cardiac symptoms was 3.2 months (3 weeks—7 months), as contrasted with 9.9 months (Table IV) for the total group.

The following case histories are illustrative of this group:

CASE 1.—History, No. 361980, D. P., a twenty-one-year-old colored girl, was brought to the admitting clinic at 2 A.M., February 12, 1932. She was obviously in great pain. When seen a few minutes later she was in collapse. She was very pale, pulseless, and no signs of cardiac activity could be elicited. Her respirations became labored, and with each gasp pink froth exuded from her nose and mouth. Emergency measures were ineffectual, and she died within fifteen minutes.

Some history was obtained from her husband. He had known her for seven years and had been married to her for the last three years. Other than an appendectomy in 1925, she had always been well so far as he knew. There had been no rheumatic manifestations. Starting five months before admission, she began to complain of pain in the epigastrium and dyspnea on exertion. She began to use two pillows at night. Three months before admission she had an attack of severe epigastric pain lasting about twenty-four hours, relieved by a hypodermic. For one month she had epigastric pain after meals, relieved by rest. For the last week she had been able to take only fluids because of the distress. Nine hours before admission she had a recurrence of the pain, similar to the attack which she had had three months before. Her physician gave her a fluid medicine, part of which she vomited. He then sent her to the hospital.

Autopsy No. 11,100. There was nothing of interest other than the heart and aorta. The heart weighed 260 grams. The epicardium was smooth. The right auricle, tricuspid valve, right ventricle, pulmonic and mitral valves and left ventricle were normal. The aortic valve flaps were slightly thickened, and the commissures were widened. The left coronary artery arose 1 cm. above the line joining the commissure, the right 2 mm. above. The orifices were almost occluded by the intimal plaques in the aorta, but there was no narrowing or occlusion in the rest of their course.

The myocardium showed no gross fibrosis.

The aorta was elastic and of normal size. Except for longitudinal wrinkling in the ascending portion, it was normal. In the descending portion, particularly the lower half, there were numerous atheromatous plaques which were calcified.

The lungs showed edema.

Microscopically, the heart muscle fibers were of normal size. There were several areas of necrosis in the myocardium, associated with inflammatory reactions.

The accompanying cellular reaction consisted in the main of elongated mononuclear cells resembling fibroblasts, many of which were in a state of mitosis. With them were a few large mononuclear ameboid cells with vacuolated cytoplasm. With the muscle necrosis, there were also a few polymorphonuclears. The blood vessels were normal.

The aorta showed the typical picture of syphilis. There was thickening of the intima with small lymphoid accumulations near the endothelium, penetrating blood vessels in the media with perivascular infiltration of lymphoid and plasma cells. Many of the vasa vasorum had greatly thickened walls.

CASE 2.—History, No. 353635, M. S., a thirty-three-year-old widowed negro housewife, was first seen on September 16, 1932, when she came to the out-patient clinic complaining of acute pain in the epigastrium radiating to both shoulders, both arms and around the heart. She had been married five years before, her husband "dying of insanity" two years later, at the age of thirty-nine years. One baby died soon after birth. The next pregnancy resulted in a miscarriage.

The patient had been perfectly well until five years before, when she married. Almost immediately she developed "womb trouble" with pain in the lower abdomen and leucorrhea. Three weeks before admission, after climbing three flights of stairs she suddenly developed terrific substernal pain which radiated through to the back and to both shoulders and arms. The pain was so bad that she fainted and was unconscious for about eight minutes. When she regained consciousness, she still had some epigastric and substernal discomfort. She stayed in bed for a day, with little relief. Since then she had had recurring attacks while walking, on eating, or on drinking cold water. With these severe attacks of pain, she would break out in a cold sweat and feel faint for a few minutes. She became dyspneic and orthopneic and for three or four nights before admission had had paroxysms of nocturnal dyspnea.

On examination she appeared to be acutely ill, crying out at intervals and holding her hand to the precordial region. The examination was negative except for the cardiovascular system. The heart was slightly enlarged. The left border of dullness was 6 cm. in the second interspace, 8 cm. in the third and 11 cm. in the fifth interspace to the left of the sternum. There were no thrills or shocks. The rhythm was regular. The rate was 80 per minute. The heart sounds were of poor muscular quality. A short systolic murmur and long blowing diastolic murmur were heard at the base in the third left interspace, transmitted over the precordium. The pulse was of the Corrigan type. The peripheral vessels were not sclerotic. The blood pressure was 172/50 in both arms. The liver was not palpable, the lungs were clear, and there was no edema of the extremities.

A leucocyte count showed 6,000 cells with 53 per cent polymorphonuclears and 47 per cent small lymphocytes. A blood Wassermann was not done.

She was immediately admitted to the hospital. Her temperature was 99.3°, pulse 74, respiration 20. While under observation, she had attacks of severe pain coming on every few minutes. Nitroglycerin gave only momentary relief. Morphine gave some relief, but the pain persisted and she began to vomit small amounts of bile-stained fluid. Twelve hours after admission she suddenly stopped breathing.

Autopsy No. 11,050. The pathological findings of interest were confined to the heart and aorta. The heart weighed 400 grams. The epicardium was smooth and glistening. The tricuspid, pulmonic and mitral valves were normal. The aortic valve cusps were thickened and retracted, and their commissures widened. The thickening of the valves was almost entirely confined to the free margins of the cusps. Here there was a rolled, considerably stiffened ridge involving the major portion of the free margin of each cusp. The bases of the cusps were normal.

The root of the aorta, for a distance of 2 cm. above the commissures, was thickened, irregularly wrinkled and contained many shallow pits and depressions. Just above the right posterior cusp of the aortic valve, the aorta was raised over an area 1 cm. in diameter, and beneath this raised area was a small accumulation of yellow material, apparently in the media. The wall about this material was gray and translucent, and beyond was a wide zone of injected vessels. The process in the base of the aorta ended sharply in a wavy line. In the remainder of the aorta, the intima contained many small elevated gray and yellow patches, most marked in the thoracic aorta. No definite longitudinal wrinkling was seen.

The mouths of the coronary arteries were markedly involved and were well above the level of the highest commissure. The right coronary had two pin-point orifices. The left coronary orifice was found to be much larger than the right, but immediately beyond the orifice, the lumen was found to be practically occluded by wrinkled, translucent, thickened intima. The distal portions of both coronaries were normally patent, and contained only a few small atheromatous plaques.

The myocardium was brownish red, firm and free from obvious fibrosis.

Microscopically the muscle fibers were somewhat increased in size. There were a few fine, fibrous scars throughout, and some sections disclosed a beginning necrosis of some of the muscle bundles. In several areas the muscle fibers appeared shrunken and their structure was indistinct. No cellular infiltration could be seen. The smaller vessels appeared to be normal.

These case histories typify that form of luetic coronary orifice involvement which may well be called the acute form of the disease. The process evidently advanced too rapidly to allow the development of an adequate collateral circulation. Clinically, the patients show many of the signs and symptoms of acute coronary obstruction. It is only in this type of case, where there is rapidly progressive narrowing of the coronary orifices, that the diagnosis can be made with any great degree of accuracy.

Mode of Death.—In the presence of aortic insufficiency, the enlarged heart may fail without showing any evidence of myocardial injury other than hypertrophy. It has been argued that partial or complete closure of the coronary orifices may also play an important rôle in producing failure. A number of reports have been published to substantiate this point, among others, those of O'Sullivan¹² and Leary and Wearn.⁶ Clawson and Bell⁵ noted that 25 patients in their series of 126 died suddenly. Of these, 15 hearts were examined. Closure of the coronary orifices was the conspicuous anatomical change found in all. While there was some hypertrophy (average 403 gm.) "it was not marked and was not of sufficient degree to be responsible for

TABLE XII

MODE OF DEATH IN 62 CASES OF SYPHILITIC AORTIC INSUFFICIENCY

	NORMAL CORONARY ORIFICES (28 CASES)	STENOSED CORONARY ORIFICES (34 CASES)
Gradual failure	6	5
Rapid failure	10	12
Sudden death	12	17

bringing about the sudden death. In these cases, death resulted primarily from the narrowing of the coronary orifices."

An analysis of the manner in which the patients of this series died is shown in Table XII.

There is a slightly greater tendency on the part of those patients with stenosed coronary orifices to die suddenly. There were 5 cases which showed extreme stenosis of both coronary openings (4 mm. or less in circumference), and the average heart weight was 370 gm. All of these patients died suddenly. On the other hand, there were 7 cases in which only one orifice showed extreme narrowing. The average heart weight in these cases was 660 gm. Only three of these individuals died suddenly. It appears that marked stenosis of both coronary orifices predisposes to sudden death.

SUMMARY AND CONCLUSIONS

One hundred and eighteen cases of cardiovascular syphilis have been analyzed to determine the bearing of coronary orifice stenosis upon the pathological and clinical picture of the disease. The degree of orifice involvement was determined by actual measurement. The method of measurement was described. It was found that the normal coronary orifice was about 10 mm. in circumference, the lower limit of normal 8 mm. The pathology and mechanism of occlusion of the coronary openings were discussed. Thirty-nine cases (33 per cent) of the 118 studied showed coronary orifices, one or both, 7 mm. or less in circumference. Of these 39 cases, 34 (87 per cent) had aortic insufficiency. These cases were then compared with 28 which showed aortic insufficiency but with no coronary orifice stenosis. The following observations were made:

1. The right coronary orifice was found to be much more frequently occluded than the left, 8 times to one.

2. An abnormally high origin of the coronary arteries appeared to be an important factor in the involvement of their orifices.

3. On the average, the hearts with stenosed coronary orifices were found to be less hypertrophied than those with patent coronary openings.

4. Infarction was relatively rare in cases with syphilitic stenosis or occlusion of the coronary artery orifices.

5. The clinical data were reviewed. Negroes were much more prone to develop stenosis of the coronary openings than were white people, 48 per cent of the negroes showing this complication as compared to 23 per cent of the white group. There appeared to be a slightly lower age level at which those cases with stenosed orifices had their initial lesions and developed their first cardiac complaints. This was found to be due to the large number of negroes in this group. The duration of life from the onset of cardiac symptoms was shorter in the patients

with stenosed coronary orifices than in the group with patent coronary openings.

6. No major differences were observed between the two groups as regarded symptoms, findings on physical examination or other diagnostic criteria. Electrocardiographic tracings in this condition were briefly discussed.

7. A clinical and pathological picture was drawn, and two cases were reported in full, illustrating the type of case with syphilitic coronary orifice involvement which lends itself most easily to diagnosis.

8. Extreme stenosis of the coronary openings due to syphilis predisposes to sudden death.

The author is indebted to Professor James W. Jobling for permission to utilize the records of the Department of Pathology.

REFERENCES

1. Warthin, A. S.: Syphilis of the Medium and Smaller Vessels, N. Y. M. J. 115: 69, 1922.
2. Maher, C. C.: Microscopic Pathology of Cardiac Syphilis, AM. HEART J. 6: 37, 1930.
3. Moritz, A. R.: Syphilitic Coronary Arteritis, Arch. Path. 11: 44, 1931.
4. Martland, H. S.: Syphilis of the Aorta and Heart, AM. HEART J. 6: 1, 1930.
5. Clawson, B. J., and Bell, E. T.: The Heart in Syphilitic Aortitis, Arch. Path. & Lab. Med. 4: 922, 1927.
6. Leary, T., and Wearn, J. T.: Two Cases of Complete Occlusion of Both Coronary Orifices, AM. HEART J. 5: 412, 1929.
7. Coombs, G. F.: Lumleian Lectures. Syphilis of the Heart and Great Vessels, Lancet 2: 334, 1930.
8. Scott, R. W.: Syphilitic Aortic Insufficiency, Arch. Int. Med. 34: 645, 1924.
9. Paré, A.: Complete Works. Translated by Thomas Johnson, London, 1649, R. Cotes and W. Dugard.
10. Morgagni, G. B.: De Sedibus et Causis Morborum per Anatomen Indogatis, Ex Typographia Remondiniana, Venice, 1762.
11. Allbutt, Sir T. Clifford: Diseases of the Arteries, Including Angina Pectoris, London 2: 21, 1915, The Macmillan Co.
12. O'Sullivan, Prof.: Material Presented at Meeting of Royal Acad. Med. of Ireland, Section of Pathol., Lancet 1: 1077, 1908.
13. Cannon, J. H.: Syphilitic Coronary Occlusion, AM. HEART J. 5: 93, 1929.
14. Lamb, A. R., Turner, K. B., Golden, R., and Von Glahn, W. C.: Cardiovascular Syphilis, Nelson's Loose-Leaf Living Medicine 4: 337, 1932.
15. Symmers, D.: Anatomic Lesions in Late Acquired Syphilis, J. A. M. A. 66: 1457, 1916.
16. Reid, W. D.: Specific Aortitis, Boston M. & S. J. 183: 67, 105, 1920.
17. Cowan, J., and Faulds, J. S.: Syphilis of the Heart and Aorta, Brit. M. J. 2: 285, 1929.
18. Quoted by Coombs, C. F.: Lumleian Lectures, Lancet 2: 228, 1930.
19. Saphir, O., and Scott, R. W.: Observations on 107 Cases of Syphilitic Aortic Insufficiency With Special Reference to Aortic Valve Area, Myocardium and Branches of the Aorta, AM. HEART J. 6: 56, 1930.
20. Carr, J. G.: Gross Pathology of the Heart in Cardiovascular Syphilis, AM. HEART J. 6: 30, 1930.
21. Wearn, J. T.: Role of the Thebesian Vessels in the Circulation of the Heart, J. Exper. Med. 47: 293, 1928.
22. Reid, W. D.: Diagnosis of Cardiovascular Syphilis, Analysis of Clinical and Postmortem Findings, AM. HEART J. 6: 9, 1930.
23. Von Glahn, W. C.: Coronary Disease and Infarct of the Heart, Proc. N. Y. Path. Soc. 23: 107, 1923.
24. Saphir, O.: Syphilitic Myocarditis, Arch. Path. 13: 266, 436, 1932.
25. Juster, I. R., and Pardee, H. E. B.: Abnormal Electrocardiograms in Patients With Syphilitic Aortitis, AM. HEART J. 5: 91, 1929.

STUDY OF GLUCOSE THERAPY IN HEART FAILURE IN ADVANCED CARDIAC DISEASE*

ABIGAIL ELIOT SMITH, M.D., AND DREW LUTEN, M.D.
ST. LOUIS, MO.

DURING the last eight years there have been many reports in the literature concerning the use of glucose in the treatment of cardiac failure. Experimentally there is evidence that the feeding of glucose results in an increase of glycogen in the cardiac muscle. In 1929, Bayliss, Mueller and Starling¹ found that insulin and glucose would prolong the life and efficiency of a heart-lung preparation. A. Valdes² in 1929 demonstrated that in fasted rabbits glucose and insulin caused the stores of glycogen in the ventricular muscle to increase in greater proportion than in any other organ or muscle. They drew attention to the possible importance of this fact in treating patients with heart disease. C. N. H. Long and G. T. Evans,³ 1932, showed that insulin and glucose given together to fasted rats caused a definite increase in glycogen in the heart, as well as in the gastrocnemius muscle. Insulin augmented the effect of glucose in the experience of all three of these groups of investigators.

Clinical evidence in favor of glucose therapy in cardiac disease has been presented by various authors since 1926. At that time there was a report by Osato⁴ in which a patient twenty-one years old with mitral stenosis and advanced heart failure was given 50 c.c. of 10 per cent glucose intravenously, with 5 units of insulin subcutaneously. Within half an hour after the injection the patient was relieved of his dyspnea and fell asleep. On the following two days he had a diuresis of 3200 and 4400 c.c. The author remarked that glucose has an "enormous therapeutic power" in severe cardiac insufficiency. In 1927 Stejskal⁵ recommended the injection of 20 c.c. of 33 per cent to 50 per cent glucose two or three times weekly in cardiac insufficiency, angina pectoris, pulmonary edema, and a variety of conditions other than cardiac. No insulin was used. No data or case reports are given. Jagic and Klima⁶ in 1927 reported definitely good results in treating pulmonary edema, angina pectoris and cardiac dyspnea with 20 c.c. of 40 per cent glucose intravenously. They advise a "small bleeding" before the injection.

In 1928 Smith, Gibson and Ross⁷ reported striking improvement in cardiac patients who were given a high carbohydrate diet.

*From the Department of Internal Medicine, Washington University School of Medicine and the Barnes Hospital.

Kisthinios and Gomez,⁸ 1930, report the results of treating cardiac failure with glucose by mouth, together with insulin subcutaneously. They administered 80 grams of glucose in the form of saturated syrup, together with 4 units of insulin. This was given every morning for eight or ten days. Their patients seemed to get temporary relief from nocturnal dyspnea and pulmonary edema.

Rimbaud, Balmès, and Martin⁹ (1931) used 50 per cent glucose by mouth, 100 c.c. per day for five days with 5 units of insulin before each dose. After five days the amounts were doubled. They found that dyspnea was relieved very promptly, within the first quarter of an hour; that diuresis began in forty-eight hours and continued with disappearance of edema. There was relief of anginal pains. Visceral stasis was not relieved effectively.

In 1932 Sprague and Camp¹⁰ reported the results of giving from 50 to 100 c.c. of 50 per cent glucose intravenously to a group of 19 patients. In congestive heart failure there was slight effect and no satisfactory diuresis. There was no effect in diphtheritic myocarditis except that the patient was "kept comfortable up to the moment of death." No effect was noted in coronary thrombosis. In two cases of paroxysmal tachycardia there was improvement; in two similar cases, none. They quote Marvin as giving the following indications for glucose therapy in cardiac disease: (1) congestive heart failure not responding to other treatment; (2) diphtheritic myocarditis; (3) coronary thrombosis in which shock is a presenting factor; (4) paroxysmal tachycardia.

The present study was undertaken with a view of determining the scope and value of glucose as an adjunct to other forms of cardiac therapy. It is a report of the use of glucose in 16 cases of heart failure in advanced heart disease. An effort was made to control the observations by keeping the patient at rest without treatment for two or three days before giving glucose. This was not always justifiable in urgent cases, in some of which glucose was given at once, and in others, digitalis. In the latter, glucose was given after the effects of digitalis had been observed. Since all the patients received both glucose and digitalis at different times, it is possible to make some comparison of the effects of the two agents in the same case.

The criteria used to estimate the effect were: first, relief of dyspnea and of pain, both subjectively and objectively; second, diuresis; third, decrease of edema and of evidence of visceral congestion; fourth, the combination of all favorable changes, i.e., restoration of compensation; fifth, any definite improvement in general condition.

Glucose was given in 5, 10, 25, and 50 per cent solutions. On several occasions from 5 to 10 units of insulin were administered fifteen minutes before the glucose. There appeared to be no striking relation of therapeutic results to the concentration of the solution or to the use or

omission of insulin. It was found that 50 per cent glucose tended to produce heavy sweating and occasionally thrombosis of veins near the site of injection. The 25 per cent solution did not cause these inconveniences and was used in the majority of cases.

The cases are presented in chronological order.

CASE 1. The patient was a white man of thirty-one years, whose presenting condition was paroxysmal tachycardia of ventricular origin. He gave a history of an attack suggestive of coronary occlusion one year preceding admission and had had several prolonged attacks of paroxysmal tachycardia during the preceding eleven months. The attack observed on admission had lasted about three weeks. Efforts to stop the attack with quinidine were only temporarily successful, and his dyspnea and weakness progressed to profound prostration with signs of circulatory failure. Four days before death he showed marked venous engorgement and a phlebotomy with removal of 325 c.c. of blood was performed. Immediately following this he was given 50 c.c. of 50 per cent glucose intravenously. The venous stasis and general prostration were slightly improved for a few hours. Heavy sweating followed the glucose injection. In the next four days he developed ascites, massive edema of the legs, and edema of the lungs, and died. At autopsy a localized myocardial scar was found, but no evidence of coronary sclerosis or of valvular disease. The etiology of the original infarction in so young a subject remained obscure. It was impossible to attribute any therapeutic effect to the glucose, other than a transient general support.

CASE 2. A woman forty-eight years old was admitted to the ward with a heart rate of 145, breathlessness, and edema. Auricular fibrillation was present. The liver was engorged and there were râles at the bases of both lungs. The patient had had no digitalis for ten days. After two days' rest in bed there was slight improvement in symptoms and the heart rate was 130. Her heart disease was thought to be due to a toxic thyroid adenoma of long standing. On two successive days she was given 100 c.c. of 5 per cent glucose preceded by 5 units of insulin. On each occasion there was transient subjective lessening of the dyspnea. The heart rate tended to rise, however, and reached 170. The edema increased and the patient gained six and one-half pounds in four days. Glucose administration was discontinued, and she was digitalized with prompt and satisfactory improvement. The edema subsided slowly and she was discharged in good condition. Subsequent observations in the out-patient department have invariably shown rapid auricular fibrillation in spite of the use of digitalis, but no evidence of congestive failure. She has declined treatment for the thyroid condition.

CASE 3. A young man thirty-one years old with a history of high blood pressure for ten years came in with marked dyspnea, orthopnea, and general anasarca. He had been in a hospital for six months and had developed massive edema two weeks before his transfer to our ward. On admission he was given 0.5 gm. of digitalis, and then was observed without medication for two days. His vital capacity was 1151 c.c. His blood pressure was 180/130. The nonprotein nitrogen was 138 mg. per cent. He was given 100 c.c. of 10 per cent glucose preceded by 5 units of insulin. The dyspnea was subjectively less, and he could lie flat. The vital capacity was 1340 c.c. but in three days he had gained four pounds. He was digitalized without effect upon the dyspnea, urine output, or edema. At this point daily injections of 100 c.c. of 50 per cent glucose were started. This produced considerable subjective relief of dyspnea and of general discomfort. The urine output was increased from 1,000 c.c. to 1,500-2,000 c.c. However, he continued to gain weight steadily with increasing anasarca. At the end of two weeks he had gained 15

pounds. Salyrgan intravenously was not effective in producing diuresis. Both the blood pressure and the nonprotein nitrogen rose, and his condition became more and more distressing. He received nine injections of 50 per cent glucose, this being the only form of therapy that seemed to yield any benefit. Each dose gave transient relief of dyspnea and general discomfort and tended to quiet restlessness, and also to improve the patient's mental outlook. In fact, there was a certain euphoria following each injection. The available veins became thrombosed, and intravenous therapy had to be given up. The patient became moribund and died ten days later. Autopsy showed chronic glomerular nephritis and cardiac hypertrophy.

CASE 4. A man, aged fifty-five years, who was definitely senile came into the ward a few hours after an early morning attack of precordial pain and dyspnea. He had had a similar attack followed by the onset of congestive failure nine months previously. On admission his blood pressure was 200/125 with pulsus alternans. Numerous râles were heard at the bases, the liver was slightly enlarged, and there was slight edema of the ankles. The electrocardiogram showed T-waves of the "coronary" type. He was observed at rest for three days. His dyspnea tended to be less and the edema of the feet disappeared, but later the dyspnea returned with cough. He was given 100 c.c. of 10 per cent glucose preceded by five units of insulin in the evening. The next day he volunteered the information that his shortness of breath and cough had been greatly relieved following the injection and that he had had a comfortable night. He looked better and was not dyspneic. The next day he developed severe substernal pain following slight exertion. He was seen to be in great distress, with yellowish pallor and cold sweat. One hundred c.c. of 10 per cent glucose with 5 units of insulin were given intravenously. During the administration he obtained relief, and his appearance improved dramatically as his color changed from yellow to a normal shade. He remarked that although the substernal pain was gone he could still feel residual pain in his elbows. Some hours later during the night the substernal pain and dyspnea returned. The next day he was again given 100 c.c. of 10 per cent glucose with 5 units of insulin which was followed by only partial relief, and did not prevent the necessity of using morphine. Administration of digitalis was then started. The following day he looked worse, and the blood pressure had dropped to 130/100. He became drowsy and unresponsive. At 4 P.M. he was given 50 c.c. of 50 per cent glucose. The following morning he reported feeling much better, and was alert and ate well, but looked pale and exhausted. He gradually declined and began to accumulate fluid. Digitalis had no effect. He became comatose and developed embolic gangrene of the left foot and died eight days after the last injection of glucose. Permission for autopsy was not obtained.

CASE 5. A colored man, thirty-one years old, with syphilitic aortic regurgitation had had dyspnea for one month and edema for two weeks. Nocturnal dyspnea was severe and was accompanied by distressing cough with blood-streaked sputum. At the time of a nocturnal attack he was given 100 c.c. of 50 per cent glucose with 10 units of insulin. This was followed by nausea and sweating, but there was definite relief of dyspnea for the rest of the night. Following a second dose on the next night there was no sickness, and dyspnea was again relieved. However, the arm veins became thrombosed. There was no diuresis, but the edema of the legs had disappeared. He was then digitalized, and there was some diuresis and partial improvement. Tubercle bacilli were found in the sputum, and he was transferred to a sanitarium.

CASE 6. A fifty-year-old negro had hypertension and uremia. His chief symptom was severe dyspnea. He was given 200 c.c. of 25 per cent glucose on two successive nights with relief of dyspnea for the night. He died a few days later. No autopsy was performed.

CASE 7. A colored woman, aged fifty years, with dyspnea and orthopnea, had a blood pressure of 276/160. There were râles at the lung bases and slight edema. She had been digitalized in the out-patient department before admission. She was given 100 c.c. of 25 per cent glucose on one occasion, from which there was no notable effect. She improved greatly while at rest and her blood pressure declined. On discharge it was 190/120.

CASE 8. A white woman, sixty-nine years old, who was known to have had hypertension for eight years, had suffered three breaks in compensation during the preceding ten months. She had been digitalized to the point of nausea ten days before admission and had received no digitalis since then. She was dyspneic, cyanotic, and orthopneic. There was massive edema. She was given 100 c.c. of 25 per cent glucose the day of admission and again the following night. There was no subjective or objective improvement, but the edema and weakness increased. She was digitalized again without improvement. She was then given salyrgan on two occasions with slight diuresis, 1300 c.c. She was discharged against advice.

CASE 9. A white woman, aged 50 years, with syphilitic aortic regurgitation was admitted to the ward, having gradually become worse upon digitalis therapy. She was digitalized to the point of minor toxic manifestations at the time of admission. She was orthopneic, had numerous râles and considerable pitting edema. She was given 100 c.c. of 25 per cent glucose, which she said was followed by a feeling of oppression in the chest, and restlessness. No immediate improvement was noted. She gradually improved on rest in bed, and the edema and orthopnea disappeared. She had practically no cardiac reserve at the time of discharge.

CASE 10. A negress thirty-four years old had syphilis of three years' standing. She had developed severe anginal attacks with dyspnea. There was no evidence of aortic insufficiency. For one week before admission she had constant dyspnea and swelling of the ankles. During an anginal attack shortly after admission she was given 100 c.c. of 25 per cent glucose with relief of pain and dyspnea. The following day the same result was obtained. She was free from attacks for three days, but on the fourth she had a severe attack of angina from which only partial relief was obtained from glucose. This was followed by an extremely severe attack two hours later. This attack and subsequent ones were promptly relieved by amyl nitrite or by nitroglycerin. Digitalis failed to abolish the attacks either of pain or of dyspnea.

CASE 11. A colored man of twenty-three years had a febrile illness in June, 1932, followed by progressive swelling of the legs and abdomen together with dyspnea and orthopnea. His condition appeared urgent on admission in December, 1932, and he was given 0.6 gm. of digitalis at 11 A.M. At 2 P.M. he was given 50 c.c. of glucose. When seen one-half hour later he was having marked respiratory distress. He began to improve in about an hour and by 5 P.M. was quite comfortable. Continued digitalization was followed by diuresis and complete disappearance of dyspnea and of congestive failure.

No signs of organic heart disease were made out upon physical examination, and the diagnosis was uncertain. Tuberculous peritonitis and tuberculous pericarditis with adherent pericardium were considered. In estimating the effect of glucose, it is notable that the improvement in dyspnea was considerably later than that usually experienced, which is during or immediately after the injection. It is possible that the change in condition at 5 P.M. was due to the digitalis (0.6 gm.) given at 11 A.M. This is borne out by his progressive and lasting improvement on continued digitalization.

CASE 12. A white man sixty-eight years old had arteriosclerotic heart disease with auricular fibrillation. On continued digitalis dosage, compensation was barely

maintained. He developed bronchopneumonia and did poorly, though heart failure was not a conspicuous feature until near the end. At a time when he appeared moribund, he was given 100 c.c. of 25 per cent glucose intravenously with decided improvement in general condition. He died five days later.

CASE 13. A colored male thirty-nine years old had syphilis with aortic regurgitation. A loud musical diastolic murmur suggested a ruptured aortic cusp. He did not do well on digitalis and was admitted to the hospital with progressive failure. There was marked respiratory distress. On two nights he was given respectively 125 c.c. and 200 c.c. of 25 per cent glucose intravenously. This was followed by relief of his distressing dyspnea for hours so that he could rest. At the same time the edema increased, and he became progressively worse and died. No autopsy was obtained.

CASE 14. A white man sixty-five years old had arteriosclerotic heart disease. Decompensation had begun six months previous to admission. Five days before admission he had a "clamping pain" in the chest and epigastrium. He was badly decompensated with orthopnea, cyanosis, massive edema and enlarged liver. He had a moderate fever and a leucocyte count of 11,800. He was given 100 c.c. of 25 per cent glucose. No improvement was observed. Digitalis also had no effect. Oxygen gave some relief of dyspnea. The patient died. A large infarct of the myocardium was found at necropsy.

CASE 15. A patient fifty-five years old, white, male, had evidence of both rheumatic and arteriosclerotic heart disease. The electrocardiogram showed auricular fibrillation and was indicative of profound myocardial damage. He showed râles at both bases, marked engorgement of the liver and slight jaundice. There was moderate edema of the legs. Urgent dyspnea was not manifest. One hundred c.c. of 25 per cent glucose with 5 units of insulin were given on three occasions. No improvement was noted. No diuresis resulted. He was discharged against advice and died within a week.

CASE 16. A white man forty-two years old with mitral stenosis was subject to attacks of cardiac asthma. Shortly after admission he developed an extremely severe attack of dyspnea of an asthmatic type which threatened to prove fatal. He was cyanotic and there was a respiratory effort with stridor. The lungs, however, remained clear, and pulmonary edema did not develop. The patient became unconscious. He was given morphine and atrophine without apparent relief. The morphine seemed to depress further the insufficient ventilation. He was put in an oxygen tent, which caused the cyanosis to clear up, but not the dyspnea and stridor. He was given 100 c.c. of 25 per cent glucose without apparent effect except that the pulse volume, which was small and failing, increased. Immediately following the glucose he was given 6 c.c. of digifolin intravenously. The circulation was supported by giving 1 minim of adrenalin intravenously every five minutes for five doses. About forty-five minutes after the intravenous digifolin, there was some improvement, and the violent dyspnea gradually passed off. Four more cubic centimeters of digifolin were given later in the day. It was thought that the improvement was due to the digifolin, the other measures possibly having served to support the patient through the critical period. This interpretation was suggested by the subsequent course. After the attack just described the patient received no further digitalis, and his dyspnea began gradually to increase three or four days later. One week after the attack he had another which duplicated the first. He was treated again with oxygen, glucose and digifolin intravenously with similar results. Thereafter he was kept on digitalis with steady improvement. There were no further attacks, and he was discharged in a fair state of compensation.

DISCUSSION

In many of the articles referred to earlier in this paper the prompt and dramatic relief of dyspnea following glucose injection or ingestion is emphasized. Relaxation and drowsiness are also mentioned, and in some cases diuresis was observed.

Of our sixteen cases of advanced heart disease with failure we noted definite lessening of the dyspnea in nine. The results were "dramatic" only in one case, Case 4. Five patients who had been restless from dyspnea got considerable relief and were able to sleep. In the other three cases relief of dyspnea was only slight, and in two of these the most notable result was improvement in general condition. In all nine the effect was temporary, lasting from three to twelve hours. Of this group five died and two left the hospital in critical condition. One did well on nitroglycerin. No progressive or lasting improvement was seen. On the contrary there was a tendency for succeeding injections to be less effective. The same statements hold true for the relief of pain of cardiac origin. There was no definite diuresis following glucose injection, even though hypertonic solutions were used. On the contrary, edema and weight were often seen to increase during glucose administration. This series includes no instances of the effect of intravenous glucose on acute pulmonary edema.

Comparison of the Effects of Glucose and Digitalis.—From the above it is apparent that in no case was glucose therapy instrumental in restoring compensation. In three cases, on the other hand, compensation was restored and maintained for an indefinite time by digitalis. These were a case of thyroid heart disease with auricular fibrillation, a case of probable tuberculous pericarditis, and a case of rheumatic heart disease with mitral stenosis. In the first two glucose had no favorable effect. In the third it probably was useful as an emergency measure. In one case of syphilitic heart disease in which there was slight improvement by digitalis, temporary relief of dyspnea was noted from glucose.

Five of the patients were not improved either by digitalis or by glucose. These cases included one of arteriosclerotic heart disease, one of coronary occlusion, one of syphilitic aortic regurgitation, one of rheumatic heart disease, and one of hypertensive heart disease. Three patients died. Two of them, one with hypertensive heart disease and one with syphilitic aortic regurgitation, were improved on bed rest so that they could be discharged. Both were complete cardiac invalids.

The mechanism by which intravenous glucose or glucose by mouth could relieve cardiac dyspnea is not entirely clear. The contraction of cardiac muscle depends not only upon oxygen but also upon carbohydrate, the supply of which theoretically may become precarious in ill-nourished states, thyrotoxicosis and probably coronary disease. The experimental work already mentioned indicated that an increased

TABLE I

RESULTS OF TREATMENT WITH GLUCOSE AND WITH DIGITALIS IN SIXTEEN CASES OF HEART FAILURE IN ADVANCED CARDIAC DISEASE

CASE NO.	AGE	DIAGNOSIS	GLUCOSE				DIGITALIS				ULTIMATE RESULT	
			RELIEF OF DYSP-NEA	RELIEF OF PAIN	DIURESIS	IM-PROVED COMPEN-SATION	GENER-AL IM-PROVE-MENT	RELIEF OF DYSP-NEA	RELIEF OF PAIN	DIU-RESIS COMPEN-SATION		IM-PROVED COMPEN-SATION
1	31	Ventricular paroxysmal tachycardia. Congestive failure.	No		Increased edema.	No	Yes	No	No	No	No	Died
2	48	Thyrototoxic heart disease. Congestive failure.	Yes		Increased edema	No	No	Yes	Yes	Yes	Yes	Discharged. Compensation restored.
3	31	Chronic nephritis and hypertension. Congestive failure.	Yes		Increased edema	No	Yes	No	No	No	No	Died
4	66	Coronary occlusion. Congestive failure.	Yes	Yes	Increased edema	No	Yes	No	No	No	No	Died
5	31	Syphilitic aortic regurgitation. Congestive failure.	Yes		No	No	No	Yes	Yes	Yes	Yes	Discharged to sanitarium.
6	50	Uremia. Hypertension.	Yes		No	No	No	No	No	No	No	Died
7	50	Hypertension. Congestive failure.	No		No	No	No	No	No	No	No	Improved on rest. Discharged.
8	69	Hypertension. Congestive failure.	No	No	Increased edema	No	No	No	No	No	No	Discharged against advice.
9	50	Syphilitic aortic regurgitation. Congestive failure.	No		No	No	No	No	No	No	No	Improved on rest. Discharged.
10	34	Syphilitic aortitis—anginal syndrome. Congestive failure.	Yes	Yes	No	No	No	No	No	No	No	Relieved by nitroglycerin. Discharged.
11	23	? tuberculous pericarditis. Congestive failure.	No		No	No	No	Yes	Yes	Yes	Yes	Compensation restored. Discharged.
12	68	Arteriosclerotic heart disease. Congestive failure. Bronchopneumonia.	No		No	No	Yes	No	No	No	No	Died
13	39	Syphilitic aortic regurgitation. Congestive failure.	Yes	Yes	Increased edema	No	No	No	No	No	No	Died
14	65	Coronary occlusion. Congestive failure.	No	No	No	No	No	No	No	No	No	Died
15	55	Rheumatic heart. Mitral stenosis. Congestive failure.	No		No	No	No	No	No	No	No	Died
16	42	Rheumatic heart. Mitral stenosis. "Cardiac asthma."	No		No	No	Yes	Yes	Yes	Yes	Yes	Compensation restored. Discharged.

supply of carbohydrate prolongs the life of the heart, augments the glycogen in the heart muscle and increases the efficiency of the musculature. On the basis of these experiments, it is thought that glucose furnishes to the exhausted heart muscle a temporarily increased supply of carbohydrate which may be stored or burned immediately, and which may have a beneficial effect on the entire circulation, including that of the respiratory center. Increased efficiency of the heart muscle would diminish the concentration of carbon dioxide and lactic acid, both of which are powerful respiratory stimulants and which tend to accumulate in the body during cardiac decompensation.

In giving from 25 to 50 grams of carbohydrate intravenously, it is evident that the increased glucose supply is of short duration and that the direct effect upon metabolism is transient. It seems that by forcing carbohydrate feeding over a longer period it might be possible to increase glycogen reserves with more lasting benefit. The results of this method, used by the authors of papers 3, 8, and 9 of the bibliography, are encouraging. However, it would appear doubtful whether daily feeding of concentrated syrups could be borne for very long, especially by patients with impairment of digestive function.

The addition of insulin seems of doubtful value in nondiabetic subjects. The amounts recommended, 5 to 10 units, would appear to be too small to cover the glucose. Moreover, larger amounts of insulin may be of some danger to patients with degenerative heart disease, especially to those with coronary disease and angina pectoris.

In our series it was noted that successive doses of glucose tended to have less effect, and after the effect of glucose had worn off the patients seemed to be worse rather than better. This may have been due to the fact that in most cases the disease was progressing to a fatal termination, but the impression was that there was exhaustion following the period of increased efficiency. Thus glucose may perhaps be classed with cardiac stimulants which increase the action temporarily and may seem to exhaust the heart in so doing. Like such drugs glucose may be most suitable to use in emergencies in which myocardial damage is slight or absent, in order to tide over a critical period, giving time for the organism to readjust itself, recuperate, or take benefit from other measures. It might at times serve to break a "vicious cycle." This suggests itself as a possible explanation of the brilliant result experienced in Osato's first trial of the method. In the same way it may be tried as a means of relief in cases of heart failure at the terminal stage, when other measures are of no avail. It may afford comfort for a time when other measures fail, and so supplement or supplant morphine. In cases of advanced chronic heart disease with congestive failure, our results indicate that intravenous glucose is not effective in restoring or maintaining compensation.

SUMMARY

1. Reports are given of sixteen cases of heart failure in advanced heart disease in which opportunity was afforded for comparison of the effects of glucose and digitalis.

2. In nine cases dyspnea was relieved to some extent. The effect, however, was of short duration (from three to twelve hours) as compared with the more lasting effect of digitalis.

3. Glucose failed to restore compensation in any case. Digitalis restored compensation in three cases.

4. The first injection of glucose seemed to have more beneficial effect than repetitions of the treatment.

5. According to the results of this study glucose therapy appears to be indicated as an emergency measure in cases of acute or urgent heart failure and in cases of advanced chronic heart failure in which digitalis in adequate amounts has not restored compensation.

REFERENCES

1. Bayliss, L. E., Mueller, E. A., and Starling, E. H.: The Action of Insulin and Sugar on the Respiratory Quotient and Metabolism of the Heart-Lung Preparation, *J. Physiol.* 65: 33, 1928.
2. Valdes, A.: Glycogen Content of Heart, Liver and Skeletal Muscle After Death, Following Injections of Glucose and Insulin, *Virchow's Arch.* 274: 361, 1929.
3. Long, C. N. H., and Evans, G. T.: Glycogen Content of the Rat Heart, *Proc. Soc. Exper. Biol. & Med.* 30: 186, 1932.
4. Osato, S.: Effect of Insulin-Glucose on Diseased Conditions Other Than Diabetes, *Ztschr. f. d. ges. exper. Med.* 51: 488, 1926.
5. Stejskal, Karl: Anwendungsgebiet, Indikationen und Dosierung der Traubenzuckerloesung, *Wien. klin. Wchnschr.* 40: 1062, 1927.
6. Jagic, N., and Klima, R.: Die therapeutische Anwendung hypertonischer Dextrose-loesungen bei Kreislauf Störungen, *Wien. klin. Wchnschr.* 40: 561, 1927.
7. Smith, F. M., Gibson, R. B., and Ross, N. G.: Diet in Treatment of Cardiac Failure, *J. A. M. A.* 88: 1943, 1927.
8. Kisthinos, N., and Gomez, D.: Action thérapeutique du sucre dans l'insuffisance cardiaque, *Presse Méd.* 38: 1363, 1930.
9. Rimbaud, L., Balmès, A., and Martin, G. A.: L'association sucre-insuline en thérapeutique cardiaque. *Presse Méd.* 39: 1647, 1931.
10. Sprague, H. B., and Camp, P. D.: Intravenous Hypertonic Glucose in the Treatment of Cardiac Disease. Preliminary Report, *New England J. Med.* 206: 288, 1932.

ELECTROCARDIOGRAMS THAT REPRESENT THE POTENTIAL VARIATIONS OF A SINGLE ELECTRODE*†

FRANK N. WILSON, M.D., FRANKLIN D. JOHNSTON, M.D., A. GARRARD
MACLEOD, M.D., AND PAUL S. BARKER, M.D.
ANN ARBOR, MICH.

INTRODUCTION

IN STUDYING the electrical field produced by the heartbeat under various circumstances, we have frequently made use of precordial leads, pad leads, and direct leads in animal experiments, and of precordial leads in clinical investigations.^{1, 2} In taking these special leads one electrode (the indifferent electrode) is placed upon one of the extremities,‡ and the other (the exploring electrode) upon the precordium, upon a large gauze pad soaked in saline and laid upon the exposed heart, or directly upon the exposed heart as the case might be. In direct leads taken in this way the potential of the exploring electrode fluctuates through so wide a range in comparison with that of the indifferent electrode that no material error is made if the potential of the latter is regarded as constant throughout the cardiac cycle. In pad leads, and particularly in precordial leads, the potential variations of the indifferent electrode, although no greater in absolute magnitude than in direct leads, are much larger in comparison with those of the exploring electrode, and play a considerably greater rôle in determining the form of the curve recorded. In standard leads the two electrodes are approximately equidistant from the heart; on the average their potential variations are of about the same magnitude and influence the form of the electrocardiogram in equal measure.

In general the curves obtained by means of the special leads mentioned are more or less helpful in solving electrocardiographic problems in proportion to the amount of information that can be gained by comparing the deflections of one lead with those inscribed in another during the same phase of the cardiac cycle. The deflections of pad leads and precordial leads are compared with each other and with the corresponding deflections of direct and standard leads. The analysis depends in the main upon the discovery of similarities, of deflections that are alike in form and correspond in time. Differences between the leads compared with respect to the relative magnitude of the potential variations of the

*From the Department of Internal Medicine, University of Michigan Medical School.

†A preliminary report based on the material incorporated in this article was published in *Proc. Soc. Exper. Biol. & Med* 29: 1011, 1932.

‡It has usually been placed upon the left leg in taking clinical curves and upon the left hind leg in animal experiments.

two electrodes tend to obscure these similarities and often make the interpretation of the curves difficult. In order to obtain deflections of similar size the string galvanometer must be made approximately ten times as sensitive when taking precordial as when taking direct leads. Deflections due to variations in the potential of the indifferent electrode are therefore ten times as large and ten times as conspicuous in the former as in the latter. The differences between direct and standard leads are even greater, and the principles followed in the interpretation of the curves obtained by means of the one cannot be applied to those obtained by means of the other.

In order to overcome these difficulties we have devised leads that record the potential variations of a single electrode. It is the purpose of this article to explain the methods adopted to achieve this end and to show that when they are followed the potential variations of the indifferent electrode are negligible.

METHODS AND APPARATUS

The method of leading referred to is illustrated in Fig. 1. Electrodes are placed upon the right arm, left arm, and left leg, in exactly the same manner as in taking

Scheme for direct measurement of potentials.

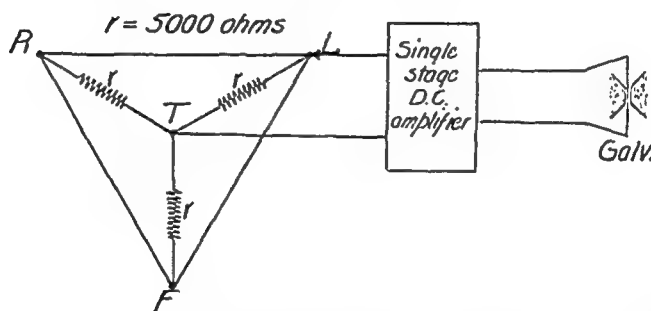


Fig. 1.—Diagram illustrating the method of leading used to record the potential variations of a single electrode. Electrodes on the right arm (*R*), left arm (*L*), and left leg (*F*) are connected through equal resistances of 5,000 ohms to a central terminal (*T*). The central terminal and an exploring electrode, or one of the extremity electrodes as indicated here, are connected to the input terminals of a vacuum-tube amplifier with a balanced plate circuit in which the string galvanometer is inserted.

the three standard leads. They are connected, each through a separate noninductive resistance (*r*), to a central terminal. The three resistances used must be equal and should be large in comparison with the largest body resistance between any two of the three electrodes. In our earliest experiments we employed resistances of 25,000 ohms, but this made our apparatus so sensitive to stray alternating currents that resistances of 5,000 ohms were finally substituted. These greatly reduced the amount of stray current picked up, and proved to be reasonably satisfactory if the skin resistance was kept sufficiently low. The central terminal serves as the indifferent electrode, and we shall show that its potential is not materially affected by the heart's electrical field. The exploring electrode may be placed upon the precordium or upon any other part of the body whose potential variations are to be

recorded. Leads from each of the extremity electrodes in succession to the central terminal are used to obtain the potential variations of the right arm, left arm, and left leg.

The central terminal and the exploring electrode are connected to the input terminals of a vacuum tube with a balanced plate circuit.* The string galvanometer is joined to the plate circuit in such a way as to include a variable resistance and a portion of the plate battery between its terminals. The value of the resistance is so adjusted that the drop in potential across it due to the plate current when the input terminals of the tube are shortcircuited is exactly balanced by the voltage drop in the included portion of the battery. When the plate current changes in response to a change in the potential of the grid with respect to that of the filament, this balance is disturbed and a small fraction of the plate current flows through the string galvanometer.

One of the chief advantages of this arrangement is the very high resistance in the input circuit. The addition of twenty-five, fifty, or even one hundred thousand ohms to the resistance in this circuit does not appreciably alter the size of the string deflection produced when an electromotive force of one millivolt is thrown into it. The tension of the string is adjusted to give the proper sensitivity at the beginning of a set of observations and usually does not need to be changed thereafter. No overshooting, due to the condenser-like effect of the skin, occurs when the skin resistance is high. The flow of current in the input circuit is so small that electrodes of almost any type can be used without fear of polarization effects. Since practically no current flows, the potential differences that it is desired to measure are not altered. The chief disadvantage lies in the difficulty of avoiding interference by stray alternating current. This is much greater than when the string galvanometer is used in the ordinary way, and it increases rapidly with an increase in the external resistance of the input circuit.

POTENTIAL OF THE CENTRAL TERMINAL

At any instant the sum of the differences in potential between the central terminal and any three electrodes connected to it is zero. The mean potential of these electrodes and the potential of the central terminal are equal. To prove these statements, let V_T represent the potential of the central terminal, and r the magnitude of the equal resistances through which it is joined to three electrodes in contact with the body. If the potentials of the three electrodes are represented by V_A , V_B , and V_C and the currents flowing from these electrodes toward the central terminal by I_A , I_B , and I_C , respectively, these quantities must satisfy the following equations:

$$V_A - V_T = rI_A \quad (1)$$

$$V_B - V_T = rI_B \quad (2)$$

$$V_C - V_T = rI_C \quad (3)$$

By adding these equations we obtain

$$(V_A - V_T) + (V_B - V_T) + (V_C - V_T) = r(I_A + I_B + I_C) \quad (4)$$

*The circuit we are using is essentially the same as that employed in Dr. W. J. V. Osterhout's laboratory at the Rockefeller Institute for Medical Research. We wish to thank Dr. Osterhout and his associate, Dr. S. E. Hill, for supplying us with a diagram of this circuit and with the data necessary for its construction.

‡Resistance external to the vacuum tube.

The right-hand side of this equation is clearly zero by Kirehkov's first law, which states that the algebraic sum of all the currents meeting at any point of a network is zero. Consequently,

$$(V_A - V_T) + (V_B - V_T) + (V_C - V_T) = 0 \quad (5)$$

or

$$V_T = \frac{1}{3} (V_A + V_B + V_C) \quad (6)$$

The same method may be used to show that if the central terminal is joined through like resistances to any number of electrodes in contact with the body, the sum of the differences in potential between it and these electrodes must be zero, and the potential of the terminal must be equal to the mean potential of the electrodes.

The difference in potential between the central terminal and any one of three electrodes connected to it may be expressed in terms of the differences in potential between that electrode and the other two. If the electrodes are placed upon the right arm, left arm, and left leg, the difference in potential between the central terminal and the leg electrode, for example, is at all times one-third the sum of the differences in potential between this electrode and the electrodes on the two arms. We may write

$$(V_C - V_T) + (V_T - V_A) = V_C - V_A \quad (7)$$

$$(V_C - V_T) + (V_T - V_B) = V_C - V_B \quad (8)$$

By equation (5)

$$V_C - V_T = (V_T - V_A) + (V_T - V_B) \quad (9)$$

If we substitute e_b for $V_C - V_A$ and e_c for $V_C - V_B$ the addition of equations (7) and (8) gives

$$V_C - V_T = \frac{e_b + e_c}{3} \quad (10)$$

In the same way it may be shown that if e_a is substituted for $V_B - V_A$

$$V_A - V_T = -\frac{e_a + e_b}{3} \quad (11)$$

and

$$V_B - V_T = \frac{e_a - e_c}{3} \quad (12)$$

In deriving the foregoing equations (1 to 12 inclusive) we have made no assumptions of any kind. It should be noted, however, that the symbols V_A , V_B and V_C appearing in these equations represent the potentials of the three electrodes in contact with the body after these electrodes have been connected to the central terminal. We desire to study the electrical field produced by the heart under natural conditions, and we must take care that our method of measurement does not modify to a material extent the quantities that we wish to measure. The heart's electrical field must be altered by any procedure that changes the resistance between points that are at different potentials. Changes in re-

sistance between points at the same potential have, of course, no effect upon the flow of current. The effects produced by attaching electrodes to the body surface must vary directly with the size and conductivity of the electrodes, and inversely with their distances from the heart; the effect of connecting these electrodes to a central terminal must vary inversely with the magnitude of the resistances used for this purpose. The extremities may be regarded as linear conductors attached to the trunk; between points on the same extremity there are no differences in potential of cardiac origin that can be detected by measurements made with the string galvanometer at the usual sensitivity. The potentials of the extremities are not, therefore, appreciably altered by placing even large electrodes upon them. The effect of connecting these electrodes to a central terminal may be neglected, if this procedure does not significantly change the potential difference between any two of them during any phase of the cardiac cycle. It will be seen that if we place our three electrodes upon the right arm, left arm, and left leg, and make the resistance r so large that connecting them to the central terminal does not materially alter the size of the deflections in the three standard leads, we shall make no serious error if we treat V_A , V_B , and V_C as if they were the potentials of these extremities before the attachment of the electrodes, and regard e_a , e_b , and e_c as the deflections in the three standard leads. It is clear that to accomplish our purpose we must make r large in comparison with the largest body resistance between any two of the three extremities. A large part of the resistance between one extremity and another is due to the resistance of the skin beneath the electrodes, and if this is kept low r may be made smaller than would otherwise be the case. It will be observed that the resistance of the skin beneath a given electrode is a part of the resistance between the subcutaneous tissues and the central terminal. When the electrodes are placed on the right arm, left arm and left leg, the resistances between this terminal and the apices of Einthoven's triangle, which are represented by the junctions of these extremities with the trunk, cannot be regarded as even approximately equal unless r is large in comparison with the skin resistance or unless the skin resistance is the same beneath all three electrodes. In practice, however, we shall know that r is large enough for our purpose if the curves taken by means of the three standard leads before and those taken in the same way after connecting the extremity electrodes to the central terminal are not significantly different.

DEDUCTIONS BASED ON EINTHOVEN'S TRIANGLE

In a previous publication² it has been shown that if the assumptions upon which Einthoven's triangle is based are valid, the potential of the

right arm (V_R), the potential of the left arm (V_L) and the potential of the left leg (V_F) at a given instant are defined by the equations

$$V_R = - \frac{e_1 + e_2}{3} \quad (13)$$

$$V_L = \frac{e_1 - e_3}{3} \quad (14)$$

and

$$V_F = \frac{e_2 + e_3}{3} \quad (15)$$

in which the deflections in standard Leads I, II, and III at the chosen instant are represented by e_1 , e_2 , and e_3 , respectively. It will be seen that at every instant

$$V_R + V_L + V_F = 0. \quad (16)$$

It should be pointed out that the derivation of these equations involves the assumption that an electromotive force generated by the heart and having a direction perpendicular to the plane of the three standard leads will not affect the potential of the right arm, left arm, or left leg. This is equivalent to the assumption that the heart lies in the plane of Einthoven's triangle.

If electrodes on the right arm, left arm, and left leg are connected to a central terminal through like and sufficiently large resistances, we may substitute V_R , V_L , and V_F for V_A , V_B , and V_C , respectively, in any of the equations in which the latter occur. It is therefore evident from equations (6) and (16) that under the circumstances specified we may, without serious error, regard the central terminal as at zero potential throughout the cardiac cycle. By connecting one of the input terminals of the apparatus, described on a preceding page, to the central terminal and the other to the right-arm, left-arm, and left-leg electrodes in succession we obtain three curves, each of which represents the potential variations of a single extremity. We may designate these curves, which are so taken that relative negativity of the extremity electrode produces an upward deflection in the finished record, by V_R , V_L , and V_F , respectively, and we shall refer to them collectively as extremity potentials. At any instant the sum of the deflections in the right-arm, left-arm, and left-leg leads must be zero. The position of the electrical axis may be determined by means of the formula

$$\tan a = \frac{\sqrt{3} V_F}{V_L - V_R} \quad (17)$$

in which a is the angle made by the electrical axis with that side of Einthoven's triangle which corresponds to standard Lead I. The curves obtained by leading from the central terminal to an exploring electrode in contact with the exposed heart, with a pad of gauze laid upon the exposed heart, or with the precordium represent the potential variations of the exploring electrode, and may be referred to as direct, pad,

and precordial potentials, respectively. The symbols V_1 , V_2 , V_3 , etc., will ordinarily be used to designate such curves.

EXPERIMENTS ON A MODEL

In order to test the conceptions at which we have arrived under conditions resembling those postulated as closely as possible, we have carried out a few experiments on a model. An equilateral triangle with sides 12.7 cm. in length was marked out on the bottom of a large shallow galvanized pan measuring 48.3 by 40.6 cm. Electrodes were placed at the apices of the triangle, and two electrodes were placed close together near its center. These central electrodes were 10 mm. apart and were so arranged that the center of the triangle was midway be-

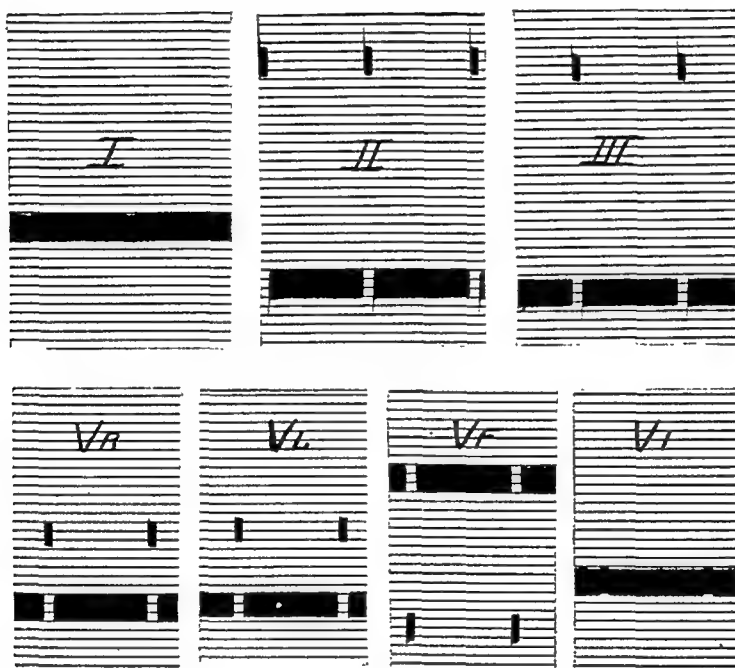


Fig. 2.—Records obtained in an experiment on a model (experiment 2, Table I). A deflection of 0.5 cm. equals one millivolt. V_1 shows the potential difference between the central terminal and a point equidistant from the central electrodes (see text) and 24 cm. from the center of the triangle.

tween them. After the pan had been filled to a depth of 38 mm. with a weak solution (about 1 per cent) of copper chloride, they were connected to a 45 volt battery through a rotating circuit breaker, which closed the circuit momentarily with each revolution. The apical electrodes were joined to a central terminal through resistances of 5,000 ohms, and the potential variations of these electrodes (V_R , V_L , and V_F) were recorded by connecting the central terminal and each of them in succession to the input terminals of the vacuum tube amplifier previously described (Fig. 2). The three leads corresponding to the three standard electrocardiographic leads were taken with the same instrument, in some instances both before and after connecting the apical electrodes to the central terminal. The potential of the central terminal was also

compared with that of points distant from the center of the triangle and equidistant from the two central electrodes; points which, theoretically, should be at zero potential. The difference in potential between such points and the central terminal was always very small.

TABLE I

EXPERIMENT	ANGLE α , $^\circ$ †	LEAD I	LEAD II	LEAD III	V_R	V_L	V_F	CENTRAL TERMINAL-DISTANT POINT
1a*	60	32.0	61.0	28.0				
1b	60	31.0	59.0	27.4	-30.0	2.0	28.5	2.0
2	90	0.2	49.0	49.0	-16.0	-16.5	32.6	0.4

Note.—The measurements given above are in tenths of a millivolt.

*In this experiment Leads I, II, and III were taken before (1a) and again after (1b) connecting the apical electrodes to the central terminal.

†The angle between the line joining the central electrodes and that side of the triangle corresponding to standard Lead I.

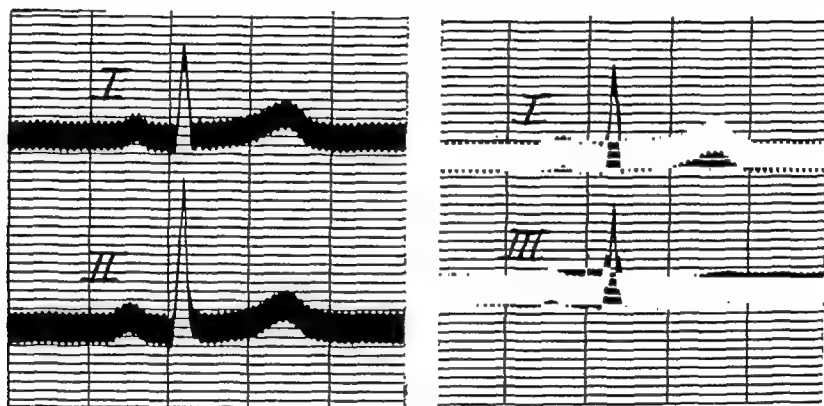


Fig. 3.—Standard electrocardiogram of a normal subject. QRS interval, 0.063 second.

The results of two experiments are shown in Table I. In the first the electrical axis was parallel to that side of the triangle corresponding to standard Lead II, and in the second it was perpendicular to the side corresponding to standard Lead I (Fig. 2). The last column of the table gives the difference in potential between the central terminal and a point near the edge of the pan and on the perpendicular bisector of the line joining the two central electrodes. In the first experiment this point was 20 cm. and in the second 24 cm. from the center of the triangle. It will be noted that the potential differences in Leads I, II, and III were somewhat greater before (1a) than after (1b) the apical electrodes were connected to the central terminal. The results of both experiments are in good agreement with the theoretical predictions based on the equations given on preceding pages.

CLINICAL CURVES

We hope in the near future to describe in considerable detail the curves obtained under various circumstances when the method of leading described in this article is employed. We shall therefore confine our

remarks here to a single illustration. The standard electrocardiograms of a normal subject are shown in Fig. 3, and the extremity and precordial potentials of the same subject in Fig. 4. It should be remembered that in the latter curves a negative variation in potential is represented by an upward, a positive variation in potential by a downward deflection of the string shadow. The curves obtained from the right side of the precordium (V_1 , V_2 , and V_E) show a small downward

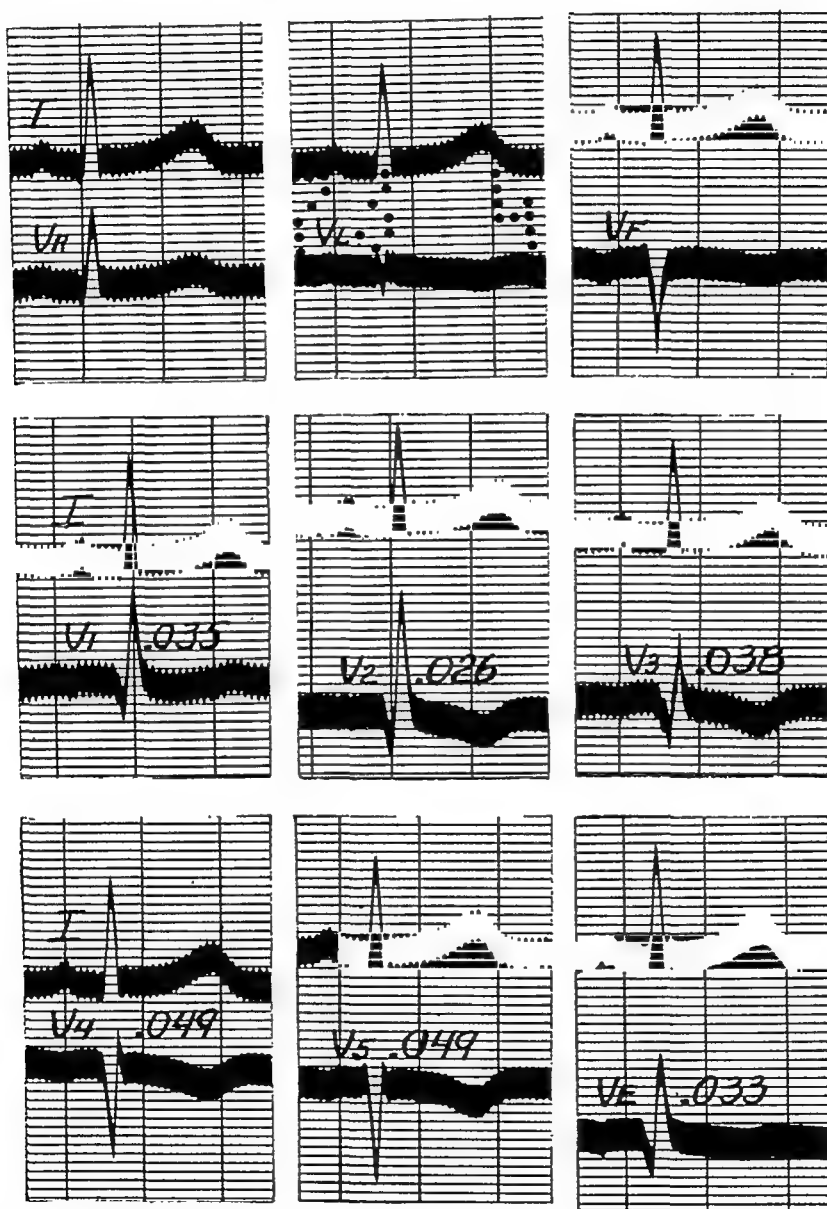


Fig. 4.—Extremity and precordial potentials of the subject whose standard electrocardiogram is shown in Fig. 3. In each instance the upper curve is standard Lead I. The lower curves represent the potential variations of the following points: V_R , right arm; V_L , left arm; V_T , left leg; V_1 , fourth rib at right sternal edge; V_2 , fourth rib at left sternal edge; V_3 , fifth rib halfway between left sternal edge and left nipple line; V_4 , fifth interspace just inside nipple line (apex); V_5 , sixth rib anterior axillary line; V_E , ensiform cartilage. In the first three records 1 cm. equals 1 millivolt; in the last six 0.5 cm. equals 1 millivolt. The figures written on the records give the position of the chief upstroke of QRS with reference to the beginning of the QRS interval.

followed by a large upward movement. The chief upstroke occurs early in the QRS interval. The curves obtained from the left side of the precordium (V_4 and V_5) show a much deeper downward movement, and the chief upstroke is late. In one of these curves (V_5) a slight rise precedes the first descent. This summit is seldom if ever large in normal subjects. The potential variations of the right arm are similar to those recorded on the right side of the precordium, and the potential variations of the left leg are similar to those recorded on the left side of the precordium. As is usually the case in normal subjects, the potential variations of the left arm are small. In left axis deviation the chief deflection of the left arm lead is downward; in right axis deviation it is upward. The direction and size of this deflection may be used as a rough index in estimating the kind and grade of ventricular preponderance. Examination of equation (14) shows that it is similar in significance to the indices used for this purpose by Lewis⁴ and by White and Bock.⁵

COMMENTS

It should be emphasized that the potential variations of the central terminal cannot be shown to be negligible unless certain assumptions are made. The assumptions referred to are those upon which Einthoven's method of determining the position of the electrical axis is based and especially the assumption that electromotive forces arising in the heart and having a direction perpendicular to the plane of the three standard leads have no effect upon the potential of the right arm, left arm, or left leg.* Some further discussion may serve to indicate the magnitude of the error that may have been introduced into our calculations by this last assumption.

Let us assume that the electrical field produced in the body at a given instant by the heart may be satisfactorily represented by the electrical field produced by a doublet located at the center of a homogeneous sphere of conducting material. At any point on the surface of such a sphere the potential due to a central doublet is proportional to the cosine of the angle between the radius drawn to that point and the axis of the doublet (Canfield,⁶ Wilson, Macleod and Barker⁷). If the axis of the doublet is parallel to the plane determined by three surface points lying at the apices of an equilateral triangle, the mean potential of these points is zero. If the axis of the doublet is not parallel to the plane mentioned, the mean potential of the three points is not zero unless this plane passes through the center of the sphere. The doublet may be regarded as the sum of two components: a doublet whose axis is parallel and a doublet whose axis is perpendicular to the specified

*Einthoven's assumption that the heart is at the center of an equilateral triangle formed by the three leads amounts to the same thing, if it is understood to mean that the heart and the three leads are in the same plane. For his purpose, however, it was necessary to assume only that the heart is equidistant from the apices of this triangle.

plane. Any difference in potential between the three points must be attributed to the parallel component. The potential due to the perpendicular component is the same at all of them and is directly proportional to the distance from their plane to the center of the sphere. This is easily understood, for this distance measures the cosine of the angle formed by the radius drawn to any one of the three points and the axis of the perpendicular doublet.

The mean potential of four surface points lying at the apices of an equilateral tetrahedron is zero, whatever the position of the axis of the central doublet may be. The potential of a central terminal connected to four such points through like resistances must also be zero, and leads from this terminal to each of these points would give the data necessary for the determination of the orientation of the axis of the doublet in three-dimensional space. We have therefore considered the advisability of connecting the central terminal in our experiments not only to the right arm, left arm, and left leg, but also to an electrode placed on the back directly behind the heart. In the case of the theoretical model under consideration the error that would be made by considering the potential of the central terminal zero would be greater or less when it was connected to the apices of an equilateral triangle than when it was also connected to a fourth point at the more distant extremity of the diameter perpendicular to the plane of the triangle according as the distance from the plane of the triangle to the center of the sphere was more or less than one-seventh of the radius.* If the four points lay at the apices of an equilateral tetrahedron, this distance would, of course, be exactly one-third of the radius.

The plane of the three standard leads is not very well defined, but it would seem that it must be regarded as passing through the heart. If this is the case, it is improbable that connecting the central terminal to an additional electrode on the back would reduce whatever error is made by considering the potential of this terminal zero. This procedure may, however, prove useful for the purpose of determining the projection of the electrical axis upon a sagittal as well as upon a frontal plane. Over other ways of doing this it has the advantage that when the distances from the heart to the electrodes are unequal the error made by assuming that the heart is at the center and the electrodes are at the apices of an equilateral tetrahedron (or triangle) may be partly or wholly eliminated by making the resistances between the central terminal and the electrodes unequal.

*The error made by using the four points specified could be corrected by making the resistance between the fourth point and the central terminal greater or less than the other three. If, for example, the distance from the plane of the triangle to the center of the sphere was exactly one-seventh of the radius it would be necessary in order to bring the potential of the central terminal to zero to make this resistance seven-thirds of the resistance between the central terminal and each apex of the triangle.

SUMMARY

In order to simplify the analysis of the curves obtained by leading from the precordium and for certain other purposes, we have devised leads that record the potential variations of a single electrode.

Electrodes are placed on the right arm, left arm, and left leg in the usual way and connected through like resistances to a central terminal. The resistances used for this purpose should be large in comparison with the resistance of the body in standard leads. Theoretical considerations and experiments on a model indicate that under these circumstances the potential variations of the central terminal are negligible.

The curves obtained by leading from an exploring electrode in contact with any part of the body to the central terminal represent the variations in potential produced by the heartbeat in the region in contact with the former. The potential variations of the right arm, left arm, and left leg are recorded by leading from the electrodes placed on these extremities to the central terminal. They may be compared with the potential variations that occur in various parts of the precordium.

To increase the resistance in the input circuit of our recording apparatus we have connected the string galvanometer to the balanced plate circuit of a one-stage vacuum-tube amplifier.

REFERENCES

1. Wilson, Macleod, and Barker: *AM. HEART J.* 7: 305, 1932.
2. Wilson, Macleod, Barker, Johnston, and Klostermeyer: *Heart* 16: 156, 1933.
3. Wilson, Macleod, and Barker: *AM. HEART J.* 7: 207, 1931.
4. Lewis: *Heart* 5: 367, 1913-14.
5. White and Bock: *Am. J. M. Sc.* 156: 17, 1918.
6. Canfield: *Heart* 14: 102, 1927.
7. Wilson, Macleod, and Barker: *J. Gen. Physiol.* 16: 423, 1933.

THE SIGNIFICANCE OF ELECTROCARDIOGRAMS CHARACTERIZED BY AN ABNORMALLY LONG QRS INTERVAL AND BY BROAD S-DEFLECTIONS IN LEAD I*

FRANK N. WILSON, M.D., FRANKLIN D. JOHNSTON, M.D., IAN G. W. HILL, M.B.,† A. GARRARD MACLEOD, M.D., AND PAUL S. BARKER, M.D.
ANN ARBOR, MICH.

INTRODUCTION

IN A previous publication¹ it was shown that the order in which the two ventricles pass into the excited state in human bundle-branch block can be determined by means of serial precordial leads. It was pointed out that such leads might be expected to prove useful in the study of the electrocardiographic changes produced by ventricular hypertrophy by coronary occlusion, and by intraventricular block. Further experience has tended to confirm this opinion. A number of cases of coronary occlusion have been studied, and the peculiarities of the precordial electrocardiogram in this condition have been briefly described.² In an experimental study of myocardial infarction recently completed it was found that the ventricular complexes of precordial, of semidirect, and of direct leads are altered in the same way. Meanwhile we have collected considerable material bearing upon the significance of various types of electrocardiograms which indicate the presence of high grade intraventricular block, but do not display all the characteristics generally considered necessary for the diagnosis of bundle-branch block. It is our present purpose to consider a group of curves that show a QRS interval measuring 0.12 second or more, a broad S-deflection in Lead I, and certain other features described on the following pages.

We have made some changes in the method of taking precordial leads described previously.¹ When we first began to make use of such leads, we placed one electrode (the exploring electrode) upon the precordium and the other (the indifferent electrode) upon the left leg. The chief features of the curves so taken are determined by the potential variations of the exploring electrode. These are usually very large in comparison with the potential variations of the indifferent electrode, but the latter cannot always be regarded as negligible. In order to reduce or eliminate them, and thus make precordial curves more nearly com-

*From the Department of Internal Medicine, University of Michigan Medical School.

†Of the Department of Medicine, University of Edinburgh.

parable to those obtained by direct and semi-direct leads in animals, we have adopted the following procedure. The indifferent electrode is replaced by a central terminal joined to electrodes on the right arm, left arm, and left leg by like resistances of 5,000 ohms or more. The central terminal and the exploring electrode are connected to the input terminals of a vacuum tube with a balanced plate circuit in which the string galvanometer is inserted. The principles upon which this method of leading is based are fully discussed in the preceding article. As is there shown, it yields curves which represent the potential variations of any part of the body in contact with the exploring electrode. This method has been used in obtaining the majority of the curves described and reproduced in this article. The curves that represent the potential variations of precordial points are designated by the symbols V_1 , V_2 , etc.; those that represent the potential variations of the right arm, left arm, and left leg are labelled V_R , V_L , and V_F , respectively. In taking the former the string galvanometer is ordinarily used at half the normal sensitivity; in taking the latter it is used at the normal sensitivity. In all these special leads the connections are so arranged that a negative variation in the potential of the exploring electrode is represented by an upward, a positive variation by a downward movement of the string shadow.

DESCRIPTION OF CLINICAL CURVES

The patient whose electrocardiograms are shown in Fig. 1 was a man, aged seventy-one years, who was under treatment in the surgical division of the hospital for carcinoma of the prostate gland with retention of urine. He had no complaints that could be referred to the heart. The systolic blood pressure was 185 mm. Hg; the diastolic pressure 90 mm. Hg. The electrocardiogram was taken at the suggestion of a consultant who found slight enlargement of the heart and a few râles at the lung bases.

Most cardiologists would probably consider the standard electrocardiograms (Fig. 1) as sufficiently characteristic to warrant a diagnosis of bundle-branch block of the rare type. The QRS interval measures approximately 0.158 second. In Lead I the R-deflection and the S-deflection are nearly equal in size, but the former is narrow while the latter is very broad. In Lead III there is an unusually prominent Q-deflection followed by a tall R, which is notched and stands upon an exceptionally wide base. The ventricular complexes in Lead II are similar to those in Lead III. The T-deflections are upright in Lead I and inverted in Leads II and III, but are relatively small in all leads.

Curves were taken from six precordial points. In the first of these (V_1), which was taken from the point farthest to the right, and in the last (V_E), which was taken by placing the exploring electrode over

the ensiform cartilage, the chief upstroke of QRS is very late. It occurs approximately 0.1 second after the first deflection in Lead I. In the curves taken from the left side of the precordium (V_3 , V_4 , and V_5), on the other hand, the chief upstroke of QRS is relatively early. It begins about 0.04 second after the first deflection in Lead I and is nearly synchronous with the peak of R in this lead. The second precordial curve (V_2) may be regarded as transitional between those taken farther to the right and those taken farther to the left; it shows both an early and a late upstroke.

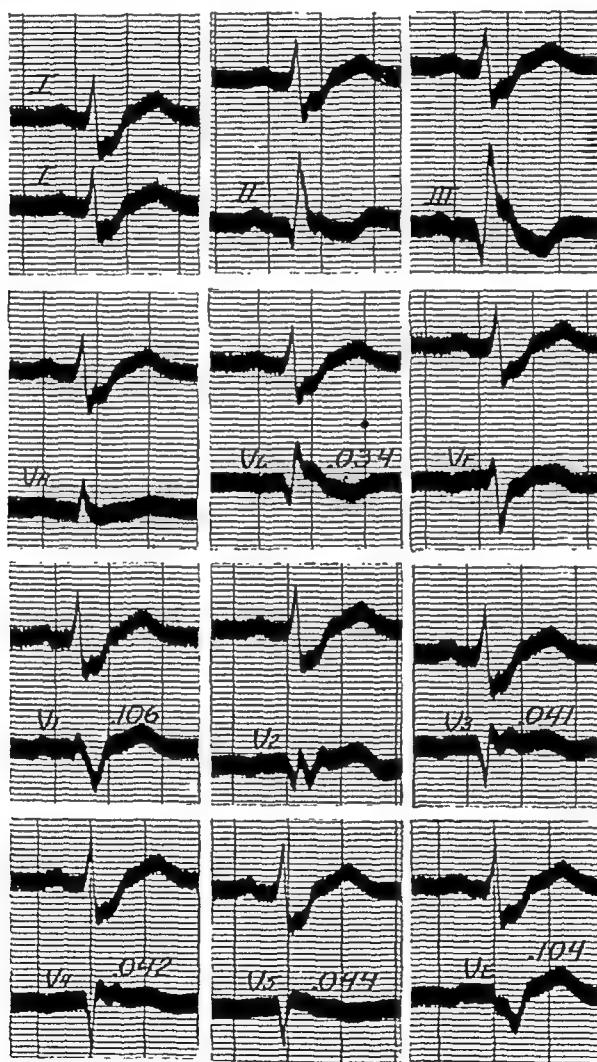


Fig. 1.—QRS interval, 0.158 second. All the figures reproduced in this article show standard Lead I (above) and a second curve (below) taken simultaneously with it. The explanatory notes of the legends refer to the lower curve only. I, Standard Lead I; II, standard Lead II; III, standard Lead III. V_1 , potential variations of the right arm; V_L , potential variations of the left arm; V_r , potential variations of the left leg. The last six curves represent the potential variations of the following precordial points; V_1 , fourth, costal cartilage, right sternal edge; V_2 , fourth interspace, left sternal edge; V_3 , fifth rib, halfway between the left sternal edge and the nipple line; V_4 , fifth interspace, left nipple line; V_5 , sixth rib, left anterior axillary line; V_6 , ensiform cartilage. A curve not reproduced from the sixth interspace in the midaxillary line is very similar to V_5 . The first six curves were taken with the string galvanometer at the normal sensitivity (1 cm. equals 1 millivolt); the last six records were taken with the galvanometer at one-half the normal sensitivity (1 cm. equals 2 millivolts). The interval in seconds from the beginning of the QRS interval to the onset of the chief upstroke of QRS, when this is well defined, is written on the records.

In this particular instance the curves that represent the potential variations of the extremities (V_R , V_L , and V_F) do not, as is often the case, closely resemble the precordial curves. The left arm curve (V_L) is somewhat like those obtained from the left side of the precordium; the main upstroke is early, and the final portions of QRS lie above the base line. The left leg curve (V_F) is more like the first precordial curve than any of the others, but its chief upstroke is earlier. The right arm curve (V_R) is small.

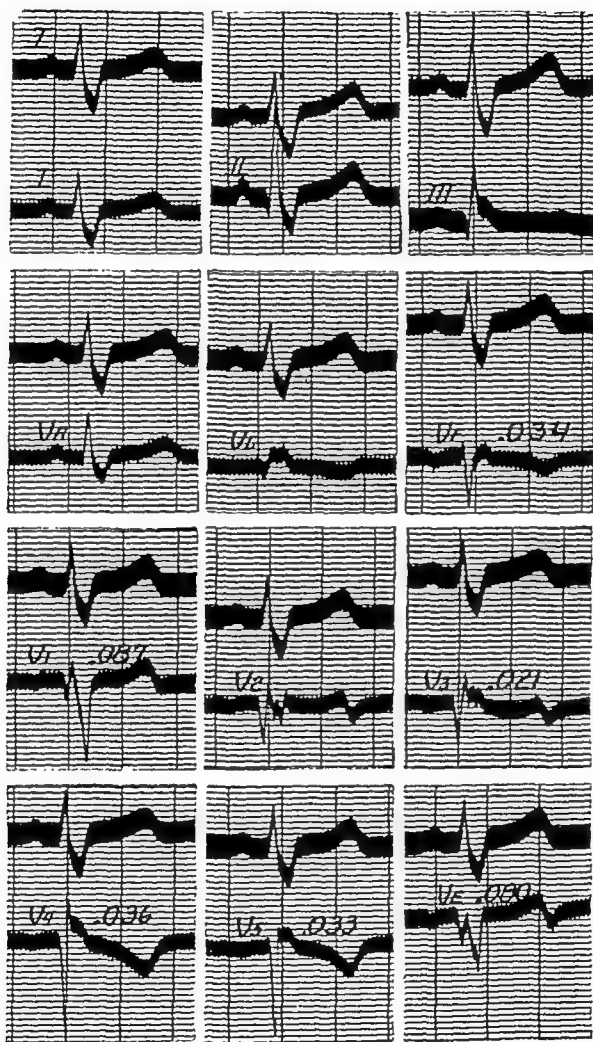


Fig. 2.—QRS interval, 0.124 second. I, Standard Lead I; II, standard Lead II, III, standard Lead III. V_R , Potential variations of the right arm; V_L , potential variations of the left arm; V_F , potential variations of the left leg. The last six curves represent potential variations of the following precordial points: V_1 , fourth costal cartilage, right sternal edge; V_2 , fourth interspace, left sternal edge; V_3 , fifth rib, halfway between left sternal edge and left nipple line; V_4 , fifth interspace, left nipple line (apex); V_5 , sixth rib, anterior axillary line; V_6 , ensiform cartilage. A curve (not reproduced) from the sixth interspace in the midaxillary line is very similar to V_5 . The first six curves were taken with the galvanometer at the normal sensitivity; the last six with the galvanometer at half the normal sensitivity.

A second set of electrocardiograms of the same type is shown in Fig. 2. The patient was a boy, aged eleven years, who was being treated for left-sided pleural effusion and acute gonorrheal urethritis.

The physical examination of the heart showed no enlargement, no valve lesions, and no other signs that could be considered abnormal. The blood pressure was normal, and there was no evidence of nephritis or of anemia. The Kahn test was negative. There was no history of rheumatic fever or other infections that might have damaged the heart, and the cause of the intraventricular block was obscure. After a month in the hospital the patient was discharged apparently quite well; the electrocardiogram had not changed.

In general outline the ventricular complexes of the standard leads (Fig. 2) are similar to those of Fig. 1. The QRS interval measures

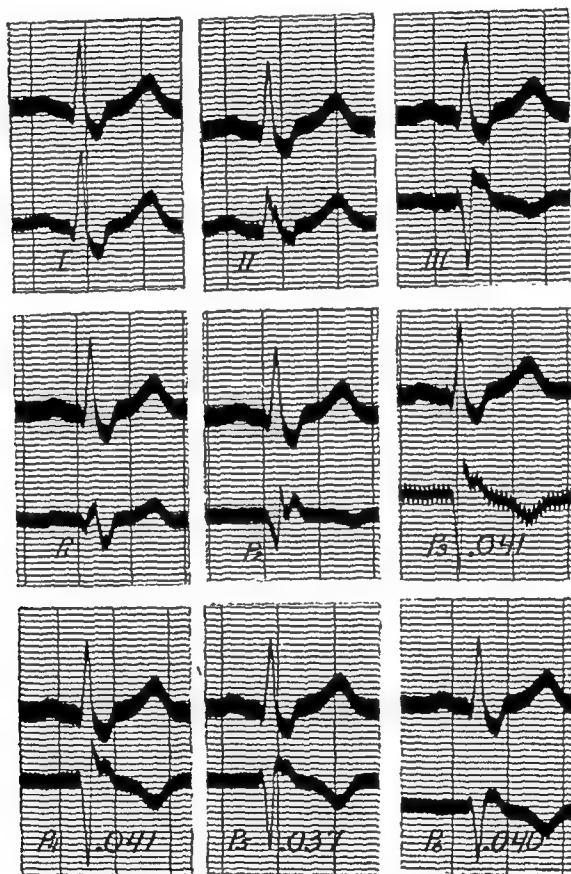


Fig. 3.—QRS interval, 0.138 second. I, Standard Lead I; II, standard Lead II; III, standard Lead III. The last six curves are precordial electrocardiograms taken by placing the indifferent electrode on the left leg and the exploring electrode on the following precordial points: P₁, third interspace, right sternal edge; P₂, third interspace, left sternal edge; P₃, third interspace, midclavicular line; P₄, fifth interspace, 3 cm. to the left of the midclavicular line (apex); P₅, fifth interspace, anterior axillary line; P₆, sixth interspace, midaxillary line. The first three curves were taken with the galvanometer at the normal sensitivity; the last six with the galvanometer at half the normal sensitivity.

approximately 0.124 second. The R spike is prominent in all three leads particularly in Lead II. In Leads I and II it is narrow, but in Lead III it is wide and notched. There is a broad S-deflection in Leads I and II, and a prominent Q in Leads II and III. The resemblance between the precordial curves and the corresponding curves of Fig. 1 is striking. The chief upstroke of QRS in the first of these curves (V₁) occurs near the end of the QRS interval, approximately

0.087 second after the first deflection in Lead I. The chief upstroke of the ensiform curve (V_E) is nearly as late. In the curves taken from the left side of the precordium (V_3 , V_4 , and V_5) the chief upstroke is almost synchronous with the peak of R in Lead I; in the different curves it begins 0.021 to 0.036 second after the first deflection in Lead I. The second precordial curve (V_2) is of the transitional variety.

The left leg curve is similar to those taken from the left side of the precordium, and the chief upstroke occurs at about the same time. The left leg may therefore be regarded as lying in the left ventricular field. The right arm curve is like the curves from the right side of the precordium, but the resemblance is not close. The left arm curve is small.

The patient whose electrocardiograms are shown in Fig. 3 was a woman, aged sixty-four years, who was under treatment in the hospital for chronic atrophic arthritis, inguinal hernia and anal fistula. She had no complaints referable to the heart, and the physical examination of the heart showed nothing abnormal except slight enlargement and accentuation of the aortic second sound. The blood pressure was normal; the Kahn test was negative.

The standard electrocardiograms (Fig. 3) differ from those of the other two patients in several respects. In Lead I the narrow R spike is much more prominent than the broad S-wave and is preceded by a small Q-deflection. In Lead III the deep downstroke is preceded by a small upward movement; a broad upward movement occurs synchronously with S in Lead I. Curves of this type are common. They have not ordinarily been attributed to right branch block. In this case the precordial leads were taken by the old method of placing the indifferent electrode on the left leg. Nevertheless they are similar in every way to the corresponding curves of Figs. 1 and 2. Here again the chief upstroke of QRS is late in the first precordial lead and early in the curves taken from the left side of the precordium. In the latter it is practically synchronous with the peak of R in Lead I and occurs about 0.04 second after the first deflection in this lead. The second precordial curve is again of the transitional type.

AN ANIMAL EXPERIMENT

The three sets of precordial curves described are strikingly similar. They are of the type that is obtained in right branch block in the dog. In order to demonstrate the resemblance between these clinical curves and experimental curves taken in the same way we may describe an experiment performed on this animal.

A large dog was fully anesthetized with morphine and ether, and the heart was exposed under aseptic precautions by the following

method. A large flap of skin and muscle in the precordium was turned back, the pleural cavity was opened by cutting through one of the interspaces, and the adjoining ribs were retracted. While respiration was maintained artificially, a small slit was made in the pericardium just below the origin of the pulmonary artery, and the right branch of the His bundle was cut by thrusting a small knife through the wall of the conus arteriosus and pressing it against the interventricular septum in the usual way. The pericardium and the chest were then carefully closed, and the animal was allowed to recover. Eight days later the dog was anesthetized with morphine and urethane and brought to the electrocardiographic laboratory. After the three standard leads had been taken, three copper disks with binding posts attached were sewn beneath the skin of the chest. These disks were arranged along a line passing across the precordium in a base-apex direction and mak-

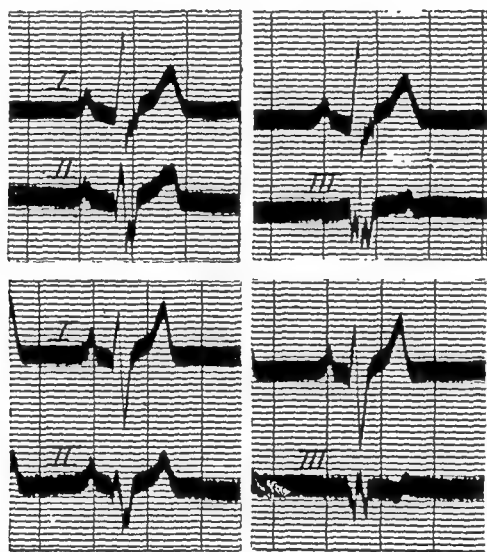


Fig. 4.—Standard electrocardiograms of a dog with bundle-branch block produced by section of the His bundle eight days before. The curves in the upper row were taken before, and those in the lower row after opening the chest. The QRS interval is approximately 0.093 second. Opening the chest altered the form of the ventricular complex, particularly in Lead I. In this lead the interval from the beginning of the QRS interval to the peak of R measures approximately 0.028 second.

ing an angle of sixty-five degrees with the midsternal line, which it crossed, 19 cm. from the episternal notch. The first disk was placed 9 cm. to the right of the midline, the second in the midline, and the third 9 cm. to the left of the midline. Using these disks as exploring electrodes two sets of leads were taken. In the first set the indifferent electrode was placed on the left leg; in the second a central terminal connected to the two fore legs, and the left hind leg through resistances of 5,000 ohms was substituted for the indifferent electrode. The two sets of curves are similar but show minor differences (Fig. 4). After splitting the sternum the pericardium was cut along a line parallel to the long axis of the heart, and the cut edges were sewn to the margins of the chest wound. The exposed heart was now cov-

ered with a pad of gauze soaked in normal saline solution, and a set of pad leads was taken. The method employed was the same as in the study of bundle-branch block¹ previously referred to except that the central terminal, instead of the left hind leg, was used as the indifferent point. The pad of gauze was then removed and a series of direct leads from the anterior surface of the heart to the central terminal, and a second set of standard leads were taken. At the end of the experiment the animal was killed, and the heart was removed and opened. A rather superficial cut crossing the course of the right

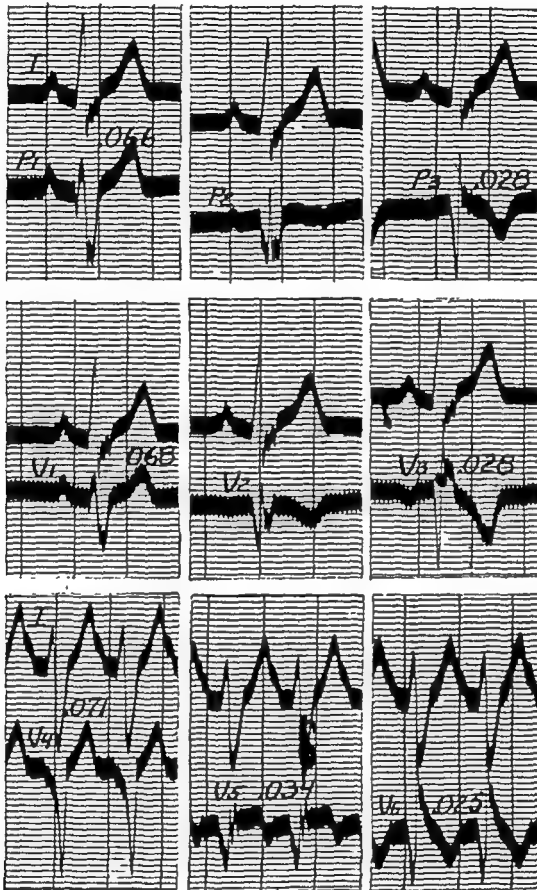


Fig. 5.—Precordial and pad electrocardiograms in experimental right branch block. In taking the first three records the indifferent electrode was placed on the left hind leg; in taking the last six a central terminal connected to the three extremities through resistances of 5,000 ohms (see text) was substituted for the indifferent electrode. In taking the curves of the second row the same exploring electrodes were used as in taking the corresponding curves of the first row. The exploring electrode for P_1 and V_1 was 9 cm. to the right of the midline; the exploring electrode for P_2 and V_2 was in the midline; and the exploring electrode for P_3 and V_3 was 9 cm. to the left of the midline. The last three curves were taken with the exploring electrode in contact with a gauze pad soaked in normal saline solution and laid upon the exposed heart. This electrode was placed upon the right basal portion of the pad for V_4 , on the central portion for V_5 , and on the left apical portion for V_6 . The first six records were taken with the galvanometer at the normal sensitivity; the last three with the galvanometer at three-twentieths of the normal sensitivity.

branch of the His bundle in its basal half and covered by a small amount of adherent thrombus was found.

The Experimental Curves.—The form of the ventricular complex in standard leads was considerably altered by opening the chest. In the

curves taken before opening the chest the ventricular complexes of Lead I are strikingly similar to the ventricular complexes of the same lead in the clinical curves we have described; R is tall and narrow, S is shallow and broad, and T is upright. In the curves taken after opening the chest the ventricular complexes of Lead I are quite different (R is much shorter and S much deeper) and resemble in general outline those usually obtained after section of the right bundle-branch. Both the curves taken before and those taken after opening the chest show much larger ventricular deflections in Lead I and much smaller ventricular deflections in Lead III than are ordinarily obtained after right branch section. Practically all the canine right branch block curves described or reproduced in the literature were taken with the chest open. Lewis³ states that restoration of the chest in his experi-

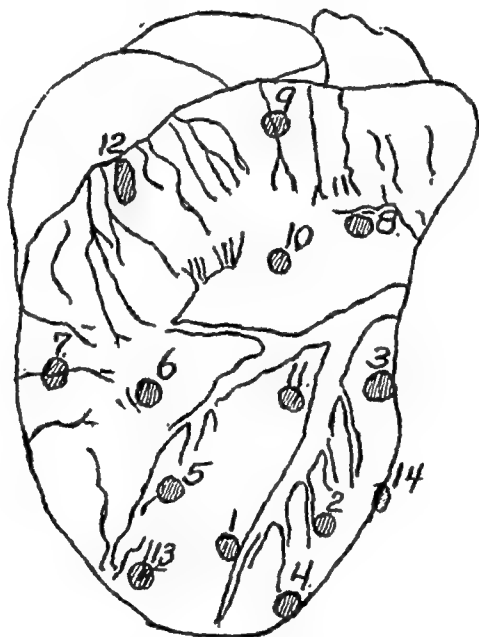


Fig. 6.—Outline drawing of dog's heart showing the location of the exploring electrode in taking the direct curves shown in Fig. 7.

ments did not alter the form of the ventricular complex materially. At the present time, however, we do not know definitely how large a part exposing the heart plays in determining the form of these curves as we know them.

The resemblance between the human and the canine precordial curves (Fig. 5) is striking. In the first precordial lead the chief upstroke is late; it occurs about 0.068 second after the first deflection in Lead I. The last precordial lead, on the other hand, shows an early upstroke practically synchronous with the peak of R; it begins about 0.028 second after the first deflection in Lead I. The ventricular complexes of the second precordial lead are of the transitional type. The pad curves are similar to the precordial curves. The chief upstroke is late in the first, which was taken from that part of the pad which lay upon

the right ventricle, and early in the last, which was taken from that part of the pad that lay on the left ventricle. In the second pad curve the chief upstroke is early, but in relative size and in shape the ventricular complexes are like those referred to as transitional.

Most of the direct curves are reproduced in Fig. 7, and the location of the points from which they were taken is shown on an outline drawing of the heart in Fig. 6. The curves taken from points on the basal portion of the right ventricle show a very late chief upstroke or in-

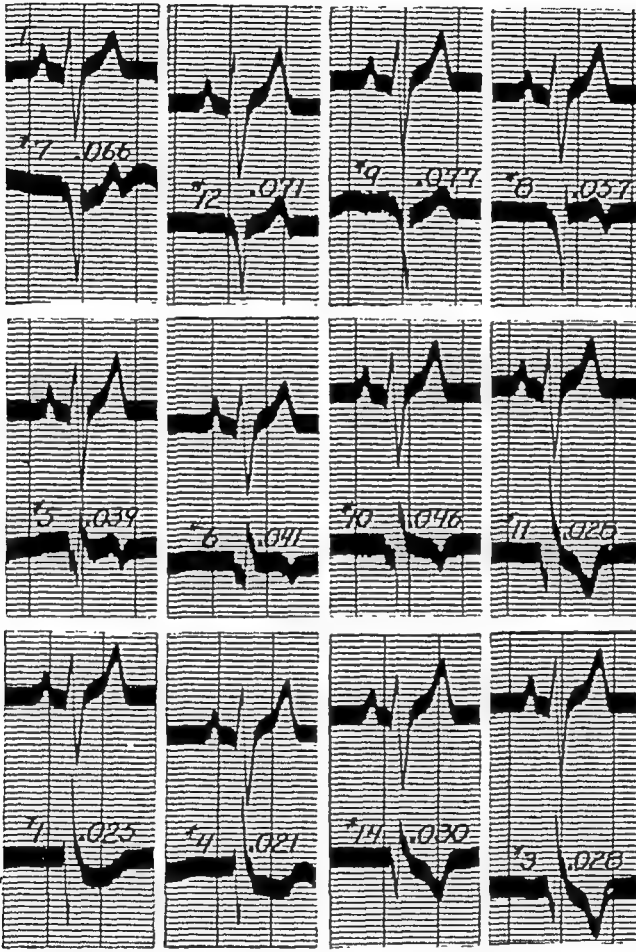


Fig. 7.—Direct electrocardiograms from the points indicated in Fig. 6. In taking these curves a central terminal connected to the three extremities (see text) was used as the indifferent point, and the galvanometer was used at one-twentieth normal sensitivity. The figures written on the records show the interval in seconds from the onset of the first deflection of the QRS group in Lead I to the chief upstroke of the direct curves. The curve (not reproduced) from point 2 is very similar to those from points 1 and 4; the curve from point 13 is very similar to those from points 5 and 6. In all figures of this article the intervals between the time lines are fifths of a second.

trinsic deflection, which begins 0.057 to 0.077 second after the first deflection in Lead I. The ventricular complexes resemble the first pad curve and that obtained from the right side of the precordium in general outline, but lack the well-defined upward movement that precedes the main downstroke in the latter.

The curves taken from the apical portions of the left ventricle closely resemble the last pad curve and that obtained from the left side of the precordium. The chief upstroke occurs 0.021 to 0.030 second after the first deflection in Lead I and is nearly synchronous with the peak of R in this lead. The direct curves show the same broad upward movement synchronous with S in Lead I that is seen in the last pad and in the last precordial curve. In these curves, however, the small upstroke that precedes the main downward movement in most of the direct curves is absent.

The direct curves from points near the attachment of the interventricular septum are somewhat variable in form. In a general way they correspond in type to the pad and precordial curves that we have classed as transitional. The chief upstroke occurs about 0.04 second after the first deflection in Lead I; the ventricular deflections are of small amplitude. These curves, however, show only one upstroke.

DISCUSSION

The striking resemblance between the direct, the pad and the precordial curves in this experiment strongly supports the view that the ventricular complex in precordial leads in man is similar in general outline and as regards the position of the chief upstroke in the QRS interval to the curves that would be obtained by leading directly from the epicardial surface of the subjacent portions of the heart wall. When there is a conduction defect that greatly delays the activation of the anterior surface of one ventricle without affecting the time of activation of the anterior surface of the other, the curves from the two sides of the precordium are, as a rule, so unlike that there is little chance of locating the conduction defect on the wrong side. There are, however, one or two features of the precordial curves obtained in branch block that are rather puzzling. In the rare type of branch block the transition from complexes showing a late chief upstroke to complexes showing an early chief upstroke generally occurs considerably farther to the right than the transition from complexes of the last to complexes of the first kind in branch block of the common variety. The principal reason seems to be that in branch block the delay in the arrival of the excitation wave at the epicardial surface is much less for those portions of the homolateral ventricle that lie near the septum than for those that are at a greater distance from it. A second peculiarity of the precordial curves in right branch block is the prominent upstroke at the beginning of QRS in the leads taken furthest to the right. This deflection occurs in canine as well as in human curves. No similar deflection is present in direct curves from the right ventricle of dogs with right branch block. For the time being the origin of this summit remains obscure.

Clinical curves of the kind described in this article are evidently due to a conduction defect that delays the activation of the anterior surface of the right ventricle; in all probability to complete right bundle-branch block. This conclusion is based upon the resemblance between the human precordial curves and those obtained in canine right branch block, and upon the resemblance between the ventricular complexes in Lead I taken before opening the chest in the experiment we have described and the ventricular complexes of the clinical curves in the same lead.

Until quite recently human branch block curves of the common type were almost universally accepted as evidence of a defect in conduction in the right branch of the His bundle. Such curves are discordant and are usually truly diphasic. In Lead I the broad initial deflection is upward and the large T-wave is inverted; in Lead III the broad initial deflection is downward and T is upright. In Lead I there may be a small Q; more often it is absent. In Lead III there is frequently a small R, but it is seldom if ever large. It was supposed that left branch block must be represented by diphasic curves of the opposite kind. Such curves proved to be exceedingly rare in comparison with those just described, and this was attributed to the difference in character between the right and left branches of the His bundle. The former is long and slender and gives off no early branches; it receives its blood supply from a single source. The latter is short and broad and branches almost at once; the more dorsal and the more ventral of its major subdivisions have a different blood supply. It seemed proper, therefore, that the right branch of the bundle should be the more vulnerable and that right branch block should be twenty or more times as common as left. It may be pointed out, however, that our ideas regarding the frequency of the two varieties of branch block depend to a very large extent upon the criteria that we set up for the diagnosis of lesions on the one side and on the other. It is probable that both right and left branch block are considerably more common than is at present believed.

In the dog the curves that represent right branch block differ from those that represent left branch block in respect to the direction of the broad initial deflection and of the T-wave in standard leads, but the two kinds of curves are not, strictly speaking, opposites. As a rule, the latter are truly diphasic, but the former are often far from it. They almost always show a very conspicuous R-deflection preceding the broad S, and the first deflection is often one-third to one-half as large, though not as broad, as the second. It may even be larger in some leads as in the instance described in this paper.* One might expect that a similar deflection would frequently be seen in human right branch block, and we believe that this is frequently the case.

*We have already pointed out that practically all canine branch block curves described in the literature were taken with the chest open. We do not know whether R in Lead I will prove to be uniformly larger when the chest is intact.

The prominent R-deflection in canine right branch block seems to be due to electric forces produced by activation of certain portions of the free wall of the left ventricle. A similar deflection in the opposite direction is absent in left branch block, probably because the free wall of the right ventricle is much thinner than that of the left. In support of this surmise regarding the origin of R in experimental right branch block we call attention to the very deep downstroke that occurs in direct leads from the apical portions of the anterior surface of the left ventricle, and in leads from the left side of the precordium. This downstroke is synchronous with R in Lead I, and it seems probable that the two deflections have a similar origin. The question arises, therefore, whether the R-deflection in Lead I and the corresponding Q or S deflection in Lead III in human right branch block do not tend to be larger when the left ventricular wall is thicker. It may be that left ventricular hypertrophy tends to modify right branch block curves in this manner.

In conclusion we believe that the clinical curves described in this article represent right bundle-branch block, and have the same significance as the discordant diphasic complexes long regarded as characteristic of branch block of the rare type.

SUMMARY

Serial precordial leads have been used in an attempt to locate the conduction defect responsible for electrocardiograms characterized by a QRS interval measuring 0.12 second or more and by narrow R-deflections and broad S-deflections in Lead I. In Lead III there is a narrow Q or S deflection synchronous with R in Lead I and a broad upward deflection synchronous with S in the same lead.

In cases in which the standard electrocardiogram is of this type precordial leads from the right side of the precordium show a very late chief upstroke; precordial leads from the left side of the precordium show an early chief upstroke approximately synchronous with the peak of R in Lead I. These curves are strikingly similar to those obtained by the same method of leading after section of the right branch of the His bundle in dogs.

For this reason it is believed that electrocardiograms of the kind mentioned represent right bundle-branch block in man. There is much less difference in frequency between clinical right and clinical left branch block than has heretofore been supposed.

REFERENCES

1. Wilson, Frank N., Macleod, A. Garrard, and Barker, Paul S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
2. Wilson, Frank N., Macleod, A. Garrard, Barker, Paul S., Johnston, Franklin D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
3. Lewis, Thomas: The Spread of the Excitatory Process in the Vertebrate Heart, *Phil. Trans. Roy. Soc. (London) Series B* 207: 221, 1916.

ELECTROCARDIOGRAMS OF AN UNUSUAL TYPE IN RIGHT BUNDLE-BRANCH BLOCK*

FRANK N. WILSON, M.D., FRANKLIN D. JOHNSTON, M.D.,
AND PAUL S. BARKER, M.D.
ANN ARBOR, MICH.

IN PREVIOUS articles^{1, 2} it has been shown that precordial leads are of great value in locating intraventricular conduction defects. The form of the ventricular deflections in such leads indicates that in man right bundle-branch block is often represented by ventricular complexes characterized by a broad S-deflection in Lead I, a simultaneous broad upward deflection in Lead III, and an abnormally long QRS interval. In this article we present evidence that it is occasionally represented by ventricular complexes of a different kind. In Lead III complexes of the type to which we refer are similar to those seen in left branch block, but in Lead I all the ventricular deflections are of low voltage and the last deflection of the QRS group is downward. Precordial leads have been employed in three cases in which the standard electrocardiogram was of this class.

CASE 1.—The first patient was a man, thirty-seven years old, who had suffered from severe bronchial asthma for the last three or four years. The symptoms were those characteristic of this condition, and the attacks were relieved by adrenalin. For the preceding month dyspnea had been almost continuous. Examination of the lungs showed emphysema, wheezing expiration, and many sibilant râles. The heart was moderately enlarged; an orthodiagram showed a frontal plane area 48 per cent larger than that found in normal subjects of similar size. The blood pressure was not increased, and no valve lesions could be detected. There was a history of chancre twelve years before, but the Kahn test was negative. Examination of the blood showed nothing abnormal. Treatment with adrenalin, ephedrine, and vaccines, and the elimination of foods that gave positive skin tests were followed by slight improvement, but frequent asthmatic attacks continued. About two months after the patient first came to the hospital, the heart rate, which had always been within normal limits, suddenly rose to approximately 180 per minute. At the same time the rhythm became conspicuously irregular. The abnormal rhythm lasted about four hours and ended, as suddenly as it began, one-half to one hour after the administration of a second 0.2 gram dose of quinidine sulphate by mouth. The first electrocardiogram was taken shortly after the onset of this attack. It shows strikingly abnormal, diphasic ventricular complexes of the discordant type. The chief deflection of the QRS group is downward in Lead I and upward in Leads II and III; there is a pronounced alternation in the amplitude of all the ventricular deflections. The ventricular rhythm is decidedly irregular. No auricular deflections can be clearly discerned. It was thought that the paroxysm was of ventricular

*From the Department of Internal Medicine, University of Michigan Medical School.

origin. An electrocardiogram taken on the following day shows normal sinus rhythm interrupted by frequent ventricular extrasystoles, which are represented by complexes similar to those recorded during the attack. In this electrocardiogram and in those taken subsequently the ventricular responses to the auricle are represented by complexes of the kind shown in Fig. 1.

In Lead I all the ventricular deflections are small. The last deflection of the QRS group is the largest and it is downward. In Leads II and III there is a small R followed by a deep broad S, and T is upright. The QRS interval is approximately 0.167 second. At first we were under the impression that these curves were an

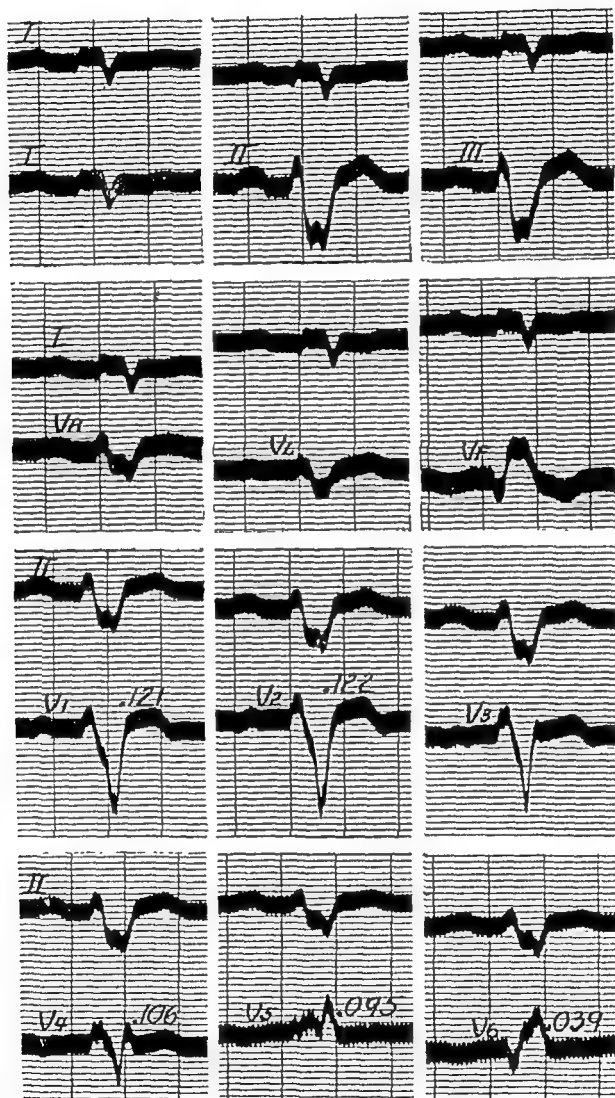


Fig. 1.—Case 1. QRS interval, 0.167 second. The upper curve of the first six records is standard Lead I; the upper curve of the last six records is standard Lead II reduced to about one-half its normal amplitude. The notes that follow refer to the lower curve of each record: I, standard Lead I; II, standard Lead II; III, standard Lead III; V_R , potential variations of the right arm; V_L , potential variations of the left leg. The last six curves represent the potential variations of the following precordial points: V_1 , fourth costal cartilage at right edge of sternum; V_2 , fourth interspace at left edge of sternum; V_3 , fifth rib halfway between left sternal edge and left nipple line; V_4 , fifth interspace in left nipple line; V_5 , sixth rib left anterior axillary line; V_6 , sixth rib left midaxillary line. The precordial curves were taken with the galvanometer at seven-tenths of the normal sensitivity (7 mm. equal 1 millivolt). The remaining curves were taken with the galvanometer at normal sensitivity. The figures written on the records give the interval from the first deflection of the QRS group in Lead II to the beginning of the chief upstroke of QRS in the lower curve. In all the records reproduced in this article the time lines indicate fifths of a second.

unusual variant of the kind seen in bundle-branch block of the common variety (left branch block), but when precordial electrocardiograms were taken, it was obvious that this was not the case.*

In the leads from the right side of the precordium (V_1 , V_2 , and V_3) the chief upstroke of QRS is very late. It occurs near the end of the QRS interval and begins about 0.12 second after the earliest ventricular deflection in Lead II. In the leads from the left side (V_5 and V_6) of the precordium the chief upstroke of QRS is somewhat earlier, but is poorly defined. The precordial electrocardiograms are similar to

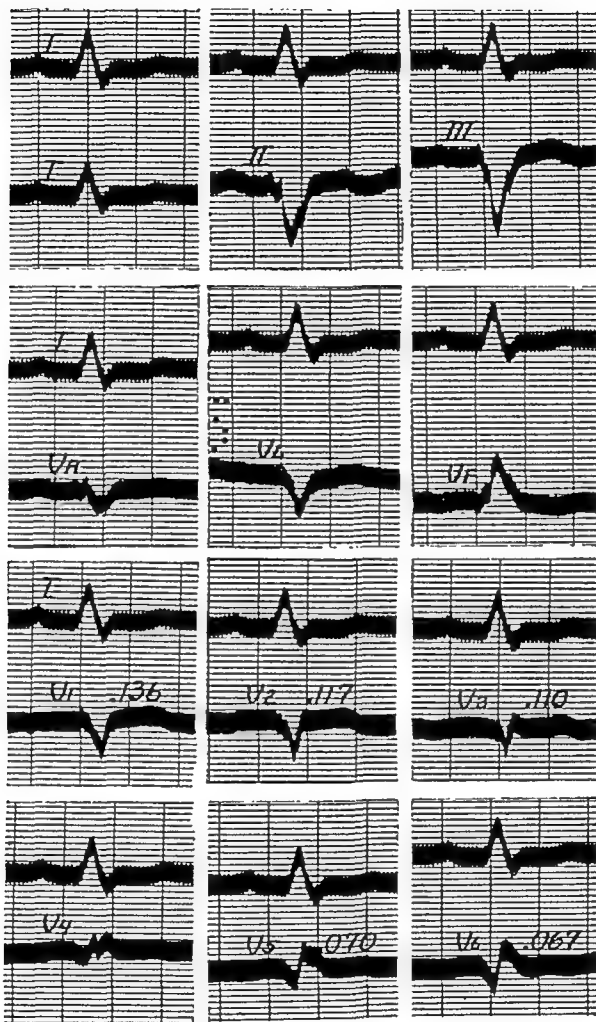


Fig. 2.—Case 2. QRS interval, 0.177 second. In each record the upper curve is standard Lead I. The notes that follow refer to the lower curves only. I, standard Lead I; II, standard Lead II; III, standard Lead III; V_R , potential variations of the right arm; V_L , potential variations of left arm; V_F , potential variations of the left leg. The last six curves represent the potential variations of the following precordial points: V_1 , fourth rib right sternal edge; V_2 , fourth interspace left sternal edge; V_3 , fifth rib halfway between the left sternal edge and the left nipple line; V_4 , fifth interspace left nipple line; V_5 , sixth rib left anterior axillary line; V_6 , sixth rib left midaxillary line. The figures written on the records give the interval in seconds between the first deflection of the QRS group in Lead I and the beginning of the chief upstroke of QRS in the lower curve. The precordial curves were taken with the galvanometer at half the normal sensitivity; the remaining curves were taken with the galvanometer at the normal sensitivity.

*In taking these precordial curves and all others described in this article, a central terminal connected to the right arm, left arm, and left leg through resistances of 5,000 ohms was used as the indifferent point. This method has been described elsewhere;³ it yields curves that may be regarded as representing the potential variations of the exploring electrode.

those that have been shown^{1,2} to be characteristic of right branch block in the dog and of branch block of the rare type in man. The chief differences are that in the present case the area over which complexes with a late chief upstroke were recorded extended somewhat further to the left than is usual, and that in the leads from the left side of the precordium the chief upstroke of QRS rises slowly and is of small amplitude. The curves that represent the potential variations of the right arm and left arm are like those obtained from the right side of the precordium; the curve that represents the potential variations of the left leg is like those obtained from the left side of the precordium.

CASE 2.—The second patient was a man, forty-eight years old, who came to the hospital complaining of attacks of unconsciousness. These attacks were of short duration and came on without warning. They were accompanied by a gripping sensation in the epigastrium, and a feeling of pressure under the sternum. The first attack had occurred four months before, and he had had several since. There was no enlargement of the heart; an orthodiagram showed a frontal plane area within normal limits. The systolic blood pressure was 125 mm. Hg; the diastolic 85 mm. Hg. The heart rate was 75 per minute and no murmurs could be detected. The heart sounds were very distant. The Kahn test and the examination of the urine were negative.

The electrocardiograms are shown in Fig. 2. The standard curves, the precordial curves, and those that represent the potential variations of the extremities are strikingly similar to the corresponding curves of Fig. 1. The QRS interval measures approximately 0.177 second. In Lead I the ventricular deflections are small. The chief deflection of the QRS group is upward, but there is a prominent deflection downward at the end of the QRS interval. In Leads II and III there is a small R followed by a deep broad S. In the leads from the right side of the precordium the chief upstroke of QRS is late; it occurs about 0.11 second after the beginning of the QRS interval. In the leads from the left side of the precordium, on the other hand, the chief upstroke of QRS occurs somewhat earlier. In these leads it begins about 0.07 second after the beginning of the QRS interval, and is somewhat better defined than in the corresponding curves of Fig. 1. The potential variations of the right and left arms indicate that these two extremities lay in the right ventricular field; the left leg was in the left ventricular field.

CASE 3.—The third patient was a farmer, aged fifty-eight years, who came to the hospital because of an inguinal hernia and shortness of breath on exertion. The latter had been noticeable for about three months, but had been worse for the past month. On one occasion some ten days before he had had to sit up all night because of nausea, vomiting, and breathlessness. Since that time there had been some pain in the precordium, but apparently it had not been severe. Ten days before coming to the hospital the patient had observed a painful red spot about two inches in diameter on the medial aspect of the lower left leg, and three or four days later the whole leg became tender. It was still red and somewhat swollen.

On examination the heart appeared to be slightly enlarged. There were no murmurs or other adventitious sounds. The heart sounds were distant. The heart rate was 80 per minute, and the rhythm was regular. The systolic blood pressure was 150 mm. Hg; the diastolic 90 mm. Hg. A few moist râles were heard at the lung bases. The condition of the left leg, which was swollen and tender, was thought to be due to venous thrombosis and thrombophlebitis. The Kahn test was negative. About three days after entering the hospital the patient suddenly began to complain of severe precordial pain, which was accompanied by profuse sweating, pallor, cyanosis, vomiting, and obvious dyspnea. It was not relieved by nitro-

glycerin, and morphine was given. On the following day there was some precordial pain and pronounced shortness of breath. The systolic blood pressure had fallen to 100 mm. Hg, and there was slight fever and a definite leucocytosis (16,000 white cells per c. mm.). After this the patient's condition was poor; he continued to complain of shortness of breath, precordial pain and vomiting. The pulse became very rapid and irregular and Cheyne-Stokes respiration frequently occurred. About one week after the attack described he had a severe chill, followed by high fever. He became moribund and died on the following night. An electrocardiogram taken soon after the patient was admitted to the hospital shows normal sinus rhythm. A second taken on the day of the attack shows sinus tachycardia (rate about 140 per

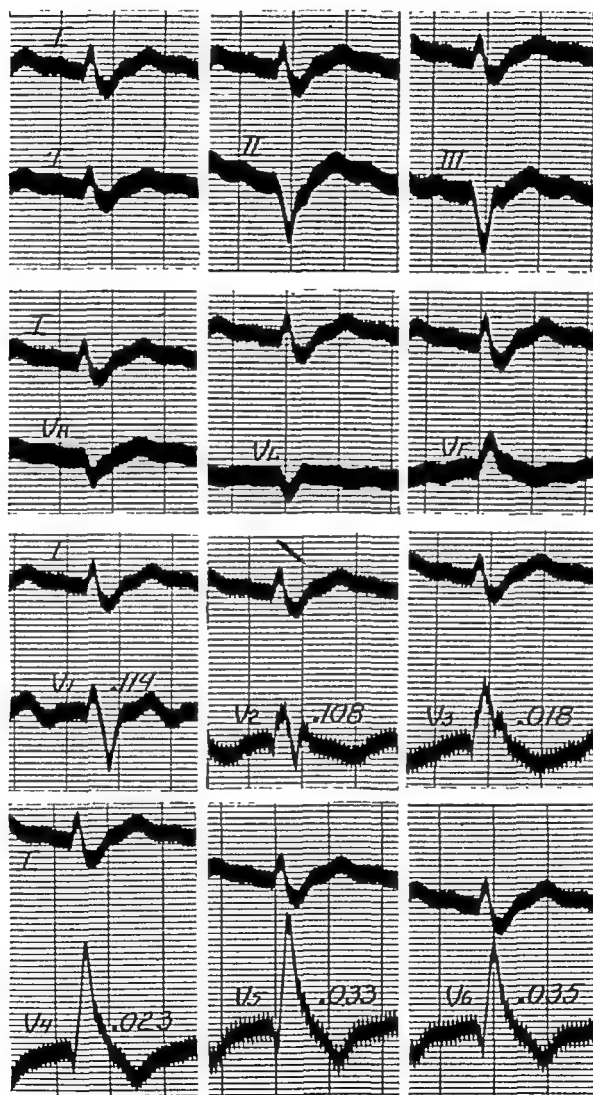


Fig. 3.—Case 2. QRS interval, 0.153 second. The upper curve of each record is standard Lead I. The notes that follow refer to the lower curves only. I, standard Lead I; II, standard Lead II; III, standard Lead III. V_R , potential variations of the right arm; V_L , potential variations of the left arm; V_F , potential variations of the left leg. The last six curves represent the potential variations of the following precordial points: V_1 , fourth rib at right edge of sternum; V_2 , fourth interspace at left edge of sternum; V_3 , fifth rib halfway between left sternal edge and left nipple line; V_4 , fifth interspace left nipple line (apex); V_5 , sixth rib left anterior axillary line; V_6 , sixth rib left midaxillary line. All of these curves were taken with the galvanometer at the normal sensitivity. The figures written on the records give the interval from the first ventricular deflection in Lead I to the beginning of the chief upstroke of QRS in the lower curve.

minute). A third taken on the following day shows frequent auricular extrasystoles; the sinus rate is approximately 100 per minute. A fourth taken four days before death shows auricular fibrillation. In all of these curves the ventricular complexes of the sequential beats are of the same form and suggest high grade intraventricular block (Fig. 3).

The autopsy showed bilateral thrombosis of the great saphenous veins, more recent on the left side, with secondary pulmonary embolism. There were many infarcts in the lungs, and this was apparently the immediate cause of death. The heart weighed 500 grams; its position in the body was not noticeably unusual. No areas of fibrosis were visible to the naked eye. On the left side of the lower septum there was a questionable change in the color of the muscle; it seemed slightly paler than the rest of the myocardium. The valves were not abnormal. The larger coronary vessels showed patchy atherosclerosis but no thrombi were found.

Microscopic examination of the heart muscle showed hypertrophy of the fibers and pronounced atherosclerosis of the coronary arteries with calcification of the media and narrowing of the lumen. There were numerous areas of fibrosis and a small area of recent softening was also seen. The areas of fibrosis were most conspicuous in the septum, and here there was also some localized impairment of the staining power of the muscle, suggesting early ischemic necrosis. The latter change was slightly more pronounced in some of the blocks from the free wall of the left ventricle.

The electrocardiograms shown in Fig. 3 were taken nine days before death. The standard curves are similar to those shown in Figs. 1 and 2. The QRS interval is approximately 0.153 second. In Lead I the ventricular deflections are small, the R and S deflections are of about the same size, but the latter is the broader. In Leads II and III, R is very small and S very deep and broad. The first precordial curve is similar to the corresponding curves of Figs. 1 and 2. The chief upstroke of QRS is late and begins about 0.1 second after the onset of R in Lead III. In the curves from the left side of the precordium the chief upstroke of QRS is early; it begins 0.02 to 0.03 second after the onset of R in Lead I. The second precordial curve is of the kind we have referred to as transitional.¹

DISCUSSION

The standard electrocardiograms in these three cases resemble some of those that have been obtained after section of the right branch of the His bundle in the dog. Right branch block in this animal is almost always represented by curves in which all the ventricular deflections of Lead I are small; in some instances R and in others S is the more prominent. In Leads II and III the chief and final deflection of the QRS group is downward. So far as Lead I is concerned, the standard curves reproduced in this article are also somewhat like those in which the ventricular complexes show a broad S-deflection in Lead I and a simultaneous broad upward movement in Lead III.² In the latter, however, the deflections of Lead I are larger; R is thinner and more prominent, and T is more definitely upright than in the former; S is conspicuous in both. The resemblance does not extend to Leads II and III; in these leads curves of the former kind are more like and cannot be easily distinguished from those that are seen in left branch block.

The precordial curves indicate clearly that in each instance the conduction defect was on the right side. They are similar to those obtained in right branch block in the dog and to those obtained in patients who exhibit diphasic ventricular complexes of the rare type or ventricular complexes with broad S deflections in Lead I.² There are certain minor differences, which may or may not be important. In Cases 1 and 2 the areas from which complexes showing a late upstroke were obtained was much larger and extended much further to the left than is usual; this is not true, however, of Case 3. The curves from the left side of the precordium lack the deep downward movement at the beginning of the QRS interval that ordinarily occurs in the same leads in normal subjects, in dogs with right branch block and in most of the patients with electrocardiograms of the kind we attribute to right branch block. In the first two cases the chief upstroke of QRS is unusually small and of unusually long duration.

It is possible that in cases of the kind described in this paper we are dealing with right branch block plus something else that modifies the ventricular complexes of the standard leads and of leads from the left side of the precordium. This additional factor, if it is really present, need not always be the same. In some cases it may be some peculiarity in the position of the heart; in others a lesion of some of the subdivisions of the left bundle-branch or infarction of the free or septal wall of the left ventricle. In Case 3 the extensive changes in the coronaries and in the left ventricular muscle found at autopsy may have played some part in determining the unusual outline of the electrocardiogram. In the other cases widespread myocardial changes were probably present, but there were no symptoms or signs suggesting myocardial infarction.

Electrocardiograms of the kind under consideration do not appear to be very common, but their real frequency is as yet unknown. An electrocardiogram that probably belongs to this class was reproduced in a recent article from this laboratory⁴ (see Fig. 20 *D*, p. 195). It was there mistakenly referred to as an atypical example of the curves seen in branch block of the common type. A large infarct involving the apical portion of the left ventricle was found post-mortem. Another curve of the same kind is reproduced in Mahaim's⁵ treatise on lesions of the His bundle (his Fig. 72, p. 242). In this instance embolic obstruction of the anterior descending branch of the left coronary artery was found at autopsy. The infarct was on the anterior and septal wall of the left ventricle. Serial sections of the bundle-branches showed lesions interrupting the right branch and the anterior subdivisions of the left. It may be pointed out that the curves reproduced in Figs. 89, 95, and 100 of Mahaim's work also show conspicuous S deflections in Lead I. In this respect they are like those reproduced in this article, and quite different from curves of the kind

we attribute to left branch block. A search of the literature would undoubtedly disclose other cases in which curves of the type under consideration were recorded (see Pardee,⁶ Fig. 18 A, p. 76).

SUMMARY

There are certain cases of intraventricular block in which the ventricular complexes of the electrocardiograms show the following characteristics: In Lead I all the ventricular deflections are small. There is a conspicuous S deflection, and T is usually flat or upright. In Leads II and III the ventricular deflections are similar in all respects to those seen in bundle-branch block of the common variety.

Precordial leads have been employed in three cases in which the standard electrocardiograms were of this kind. In these leads the ventricular complexes are like those that are recorded in dogs with right branch block and in patients with diphasic ventricular complexes of the rare type. It is thought that the curves referred to represent right branch block. Some additional factor that modifies the form of the electrocardiogram may be present.

REFERENCES

1. Wilson, Macleod, and Barker: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
2. Wilson, Johnston, Hill, Macleod, and Barker: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *AM. HEART J.* 9: 459, 1934.
3. Wilson, Johnston, Macleod, and Barker: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
4. Wilson, Macleod, Barker, Johnston, and Klostermeyer: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
5. Mahaim, Ivan: *Les Maladies organiques du faisceau de His-Tawara*, Paris, 1931, Masson et Cie.
6. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, New York, 1933, ed. 3, Paul B. Hoeber, Inc.

PRIMARY SARCOMA OF THE HEART

REPORT OF A CASE WITH ELECTROCARDIOGRAPHIC AND PATHOLOGICAL STUDIES*†

ARLIE R. BARNES, M.D., DONALD C. BEAVER, M.D.,
AND ALBERT M. SNELL, M.D.
ROCHESTER, MINN.

INVASION of the heart by a neoplastic process, whether primary or secondary, is relatively rare. Lymburner, in a review of 8,550 post-mortem examinations at The Mayo Clinic, found 4 cases of primary tumor of the heart, and in 52 cases the heart was the site of metastatic invasion by neoplasms. Adami stated that the relative immunity of the heart to neoplastic involvement "is probably to be attributed to the fact that the heart, above all organs, is constantly in a state of great efficiency, well-nourished, well-innervated, and functionally always active." The rarity of cardiac neoplasms is attested by the fact that Lymburner found only 226 cases of primary tumors of the heart recorded in the literature, to which he added 4 cases. The first reports of cases are attributed, by Beck and Thatcher, to Zollicofferus (1685) and Theophy Boneti (1700). According to Perlstein, the first authentic modern cases are those of Albers (1835) and Bodenheimer (1865). In recent years, a number of writers have reported additional cases and have reviewed the literature; among the more important reviews of this type are those of Perlstein, Beck and Thatcher, Meroz, Uehlinger, Karrenstein, Goldstein, Bradley and Maxwell, Diebold, Pommer, and Matras. The consensus of opinion of these writers is that the majority of primary cardiac tumors are of mesenchymal origin, and may be classified as spindle-cell, round-cell or mixed-cell sarcomas, the first-named being the type most commonly encountered; a few rhabdomyosarcomas have also been noted. The primary focus of these tumors is variable. Beck and Thatcher cited Link's series of cases, and noted the relatively high incidence of primary involvement of the auricles; the ventricles, valves, and intra-auricular septum are considerably less common as primary sites.

The symptoms of these tumors are, as one might expect, as variable as is their distribution. Numerous analyses of the symptoms have been made, but no constant clinical syndrome can be said to have been established. As Meroz has pointed out, there can be no characteristic symptoms if the tumor does not interfere with the cardiac mechanism.

*Submitted for publication November 23, 1932.

†From the Sections on Cardiology and Pathologic Anatomy and the Division of Medicine of the Mayo Clinic.

He went on to state that if the valve orifices are involved, stenosis, regurgitation, or both, may result, and the pulmonary and general circulation may be involved singly or in combination. If the pericardial surface is involved, an effusion, usually hemorrhagic, results; involvement of the cavities may produce multiple embolic phenomena, and involvement of the conduction system may produce arrhythmia of various types. Meroz' conception of the symptoms of cardiac tumors is based chiefly on hypothetical grounds. Nowicki, Bradley and Maxwell, Matras, and others, from a study of case records, have outlined the symptoms most commonly recorded in the literature. Among these may be mentioned: (1) progressive circulatory failure, for which no obvious anatomical basis can be demonstrated; (2) progressively increasing valvular stenosis, with murmurs which change on movement or from day to day; (3) signs of mediastinal tumor, sometimes associated with gross changes in the appearance of the heart on roentgenological examination; and (4) recurrent hemorrhagic pericardial or pleural effusions.

So far as we are able to judge from available reports in the literature, the diagnosis of a primary cardiac neoplasm has not been made during life. Lymburner reviewed 4 cases in which secondary tumors of the heart had been recognized during life, including the case reported by Willius and Amberg in 1921. The case reported here is of particular interest because the coexistence of signs of pericarditis, heart-block, and metastasis to the muscles of the shoulder girdle permitted a tentative clinical diagnosis of malignant involvement of the heart. Curiously enough, the two principal diagnostic points in this case, heart-block and metastasis to the skeletal system, appear to be particularly uncommon. Bradley and Maxwell stated that heart-block has been noted in two cases, and Goldstein cited the case of Armstrong and Monckeberg, in which this condition developed in an infant with a cardiac tumor. In Beck and Thatcher's case a metastatic deposit was noted in the right deltoid muscle. In Perlstein's series of thirty cases, metastasis was noted in the lungs, liver, pancreas, and mediastinal lymph nodes, and in the suprarenal glands, but not in the skeletal system. The diagnosis in this case is therefore no contradiction of the often-quoted statement that diagnosis of a cardiac tumor is "either impossible or a matter of good fortune."

CASE REPORT

A woman, a housekeeper, aged sixty-two years, was admitted to St. Mary's Hospital December 10, 1932, because of pain in the thorax and dyspnea on exertion. These symptoms had been present for about two months and had been accompanied by definite loss of weight and strength. For about one month she had suffered from night sweats, and was known to have had a daily rise in temperature to 100° or 102° F. The past history was entirely irrelevant to the complaint at the time of admission.

Physical examination gave evidence of considerable loss of weight, and the patient was decidedly ill. The temperature was 102° F., and the pulse rate 120 beats each minute. Cyanosis or peripheral edema could not be made out, but definite orthopnea was present. There were no oral foci. Examination of the lungs gave essentially negative results. There were no significant abdominal findings, except some tenderness in the upper end of a previous laparotomy scar. Examination of the pelvis gave essentially negative results, except for evidence of menopausal involutionary change. The principal physical findings concerned the heart. It was not enlarged, the tones were clear, and definite valvular murmurs could not be heard. Loud friction sounds were heard all over the precordium, varying somewhat on change in the patient's condition. Results of urinalysis and serological test for syphilis were negative. The concentration of hemoglobin was 11.4 gm.; erythrocytes numbered 4,390,000 and leucocytes 6,200 in each cubic millimeter of blood. A roentgenogram of the thorax revealed a calcified tuberculous process in the upper lobe of the left lung. Two cultures of the blood did not reveal growth in forty-eight hours. An agglutination test for *Alcaligenes abortus* was negative. Electrocardiographic examination disclosed a rate of 106, sinus tachycardia, exaggerated P-wave in derivation II, and slurred QRS complexes in derivations II and III.

A diagnosis of subacute, fibrinous pericarditis was made, but no explanation was advanced at the time as to its etiology. Because of its probable infectious nature, however, a course of sodium cacodylate was begun, the dosage consisting of 7½ grains (0.48 gm.) given intravenously twice daily. Five days later the pericardial friction sounds were altered; in fact, with the patient in the sitting position they were almost inaudible. There were no signs of pericardial effusion, and she was definitely better. December 22 the pericardial friction sounds had completely disappeared, and the temperature remained below 100° F. for twenty-four hours. Administration of sodium cacodylate was discontinued at this time. On this date the pain in the thorax was entirely relieved, but on December 26 it reappeared, and the temperature began to become elevated in the afternoon to about 102° F. Another course of sodium cacodylate was begun, but within three days a diffuse, arsenical type of dermatitis developed, which compelled us to abandon this form of treatment. The dermatitis cleared rapidly under treatment, and caused the patient no serious inconvenience.

On January 3, 1933, it was noticed that the cardiac tones were much less distinct, especially in the region of the apex. There were no definite signs of pericardial effusion, and roentgenograms of the thorax did not reveal significant widening of the cardiac shadow. An electrocardiogram made on this date revealed a rate of 116, left ventricular preponderance, diphasic T-wave in derivations I and II, notched P-wave in derivation II, and notched QRS complexes in derivation III. Culture of the blood did not reveal growth in forty-eight hours.

On the night of January 5 acute pain developed in the region of the right shoulder. On the following morning the joint was painful to touch, and there was a moderate amount of induration along the posterior border of the deltoid muscle. Local treatment with hot packs, and full doses of salicylates given during the next few days failed to have any effect on this condition, and by January 9 the joint was swollen, hot, and indurated. A tentative diagnosis of metastatic abscess of the right deltoid muscle was made, and after a further period of observation of three days, the muscle was incised under procaine anesthesia. The muscular substance was edematous and indurated, but a definite abscess could not be found. Tissue cultures were made; and a specimen was removed for biopsy. On pathological examination this revealed very evident involvement of the muscle with malignant cells, but these were so un-

differentiated that a definite conclusion could not be reached as to their probable source. The cultures did not reveal growth of organisms. During the next four or five days there was little change in the patient's condition. The pain in the thorax and shoulder continued, and the pericardial friction sounds continued to be definitely audible at times and absent at others.

On the morning of January 18 considerable edema was present in the left arm, the lumbodorsal region, and both lower extremities. The cardiac rhythm, which previously had been regular, was greatly altered, and gross irregularity was noted. An electrocardiogram was made at once, and this gave evidence of an auricular rate of 116 and a ventricular rate of 86, with complete auriculoventricular dissociation. On the following day the cardiac rhythm became regular, but the electrocardiogram revealed a prolonged auriculoventricular conduction time of 0.32 seconds. A diagnosis of tumor of the heart, with involvement of the conduction system and pericardium, and with metastasis to the right deltoid muscle was suggested. Because of the uncertainty with regard to the previous biopsy, another specimen was taken from the same region. A somewhat more satisfactory biopsy was obtained from the muscle, which on examination revealed a highly undifferentiated, infiltrating, degenerating cellular tumor, probably a sarcoma. This development appeared to establish definitely the diagnosis of sarcomatous involvement of the heart. Owing to the patient's greatly weakened condition the search for a primary source was necessarily curtailed, and the results were entirely negative. Repeated roentgenological examinations of the thorax and a series of cultures of the blood gave no significant results. Electrocardiograms were made January 21, 23, 25, and 27, all of them giving evidence of complete auriculoventricular dissociation. The peripheral edema, which had been noted previously, increased slowly. The patient became more and more stuporous, and roused only to complain of pain in the affected shoulder. She took almost no food, and appeared to fail very rapidly. A course of radium therapy was given over the right shoulder in the hope of relieving the pain and perhaps of effecting slight temporary improvement in her general condition. She was transferred to her home by ambulance January 31, when the treatment with radium had been completed. Her course there was marked by progressive failure and increasing edema and orthopnea, as well as by other signs of circulatory failure. Death occurred February 14. Examination shortly before death gave no further clinical evidence of sarcomatosis, except some rather questionable nodules in the region of the left deltoid muscle.

Necropsy.—Necropsy was performed five hours after death. The body was extremely emaciated, and the lower extremities were markedly edematous. Multiple purpuric patches were present on the skin of the face and forehead. The skin of the right arm, overlying the deltoid muscle, was thickened and revealed multiple firm, fixed, small, shotlike, subcutaneous nodules, by palpation. In both pleural cavities there was clear, dark amber fluid, 500 c.c. in the right cavity and 1,000 c.c. in the left. The pericardial cavity was obliterated, partially by fibrous and fibrinous adhesions between the parietal and visceral layers, but also by the interposition of soft, grayish white, neoplastic tissue. The neoplastic tissue appeared to arise from both parietal and visceral layers, and to be entirely confined within the sac; the external surface of the parietal pericardium was smooth, glistening, and apparently free from tumorous involvement. On manual separation of the pericardial surfaces, the internal parietal surface and the visceral surface disclosed multiple grayish white, relatively soft, slightly elevated, plaque-like masses of tissue. These were so numerous that diffuse involvement was approximated, but where discrete, these areas were from 2 mm. to 5 mm. in irregular diameter (Fig. 1).

The heart and adherent pericardium weighed 325 gm. The wall of the right auricle was diffusely thickened and replaced by relatively soft, friable, grayish white tissue, which was contiguous with similar appearing tissue of the epicardium. Although the auricular wall appeared to be diffusely involved, there were some areas which were distinctly nodular. These were especially prominent above the posterior cusp of the tricuspid valve, where the endocardium was eroded by tumor. Here the tumor extended somewhat into the auricular chamber, as slightly elevated and roughened nodules; the two largest of these were each 1 cm. in diameter. Elsewhere the endocardium of the auricle was smooth and apparently not extensively invaded; where considerable tumor tissue existed in the wall, however, there was an evenly rounded bulging of the corresponding portion of the wall toward the auricular chamber. This was especially the case in the region of the interauricular septum, below the foramen ovale. The thickness of the wall of the right auricle was usually 0.5 to 1.5 cm., but at the septum it was 2.5 cm. thick. The tricuspid



Fig. 1.

Fig. 2.

Fig. 1.—Neoplastic involvement of the pericardium over the posterior portion of the left ventricle. The pericardium has been reflected from the epicardium.

Fig. 2.—Involvement of the right auricle and right ventricle by the neoplasm. The tumor of the auricle is particularly prominent above the tricuspid valves. Most extensive involvement of the right ventricle appears on the interventricular wall; an incision appears through the center of this area.

valves were normal. The wall of the right ventricle was involved in a way similar to that of the right auricle, but the involvement was less extensive. There was diffuse, grayish white, neoplastic infiltration of the ventricular muscle below the posterior papillary muscle, extending downward to the apex, and anteriorly to the base of the anterior papillary muscle; the tumor extended toward the left in the interventricular septal portion of the right ventricle, as far as the papillary muscle of the conus. Most of the neoplastic change observed in the right ventricle was in this portion. There was no tumor observable in the anterior wall (except near the apex) in the region of the conus arteriosus, in the base beneath the tricuspid valves, nor in the extreme left portion of the septal region. At the apex, the wall of the right ventricle was 1.5 cm. thick; elsewhere the thickness averaged 0.8 cm. Nowhere in the right ventricle did the tumor extend through the endocardium. The

pulmonary valves were normal. (Fig. 2.) The left auricular wall was invaded by neoplasm only in the region of the interauricular septum and the auricular appendage. The wall of the appendage was 1 cm. thick. Elsewhere, except in the interauricular septum, the wall of the left auricle was 1 to 2 mm. thick. The mitral valves were normal. The left ventricle was normal; its muscle was approximately 1 cm. thick. The aortic valves were normal. The large vessels, to and from the heart, were normal, without neoplasm surrounding them, except in their intrapericardial portion.

Both lungs revealed numerous very small, mostly subpleural, metastatic nodules, the largest of which was 1.5 cm. in diameter. The thymus gland was replaced by adipose tissue; there were no metastatic nodules. About the arch of the aorta, and the bifurcation of the trachea, some lymph nodes were enlarged. In one region the nodes were conglomerate and formed a firm, grayish white mass 3 cm. in diameter. Lymph nodes elsewhere were somewhat enlarged, but on gross inspection disclosed

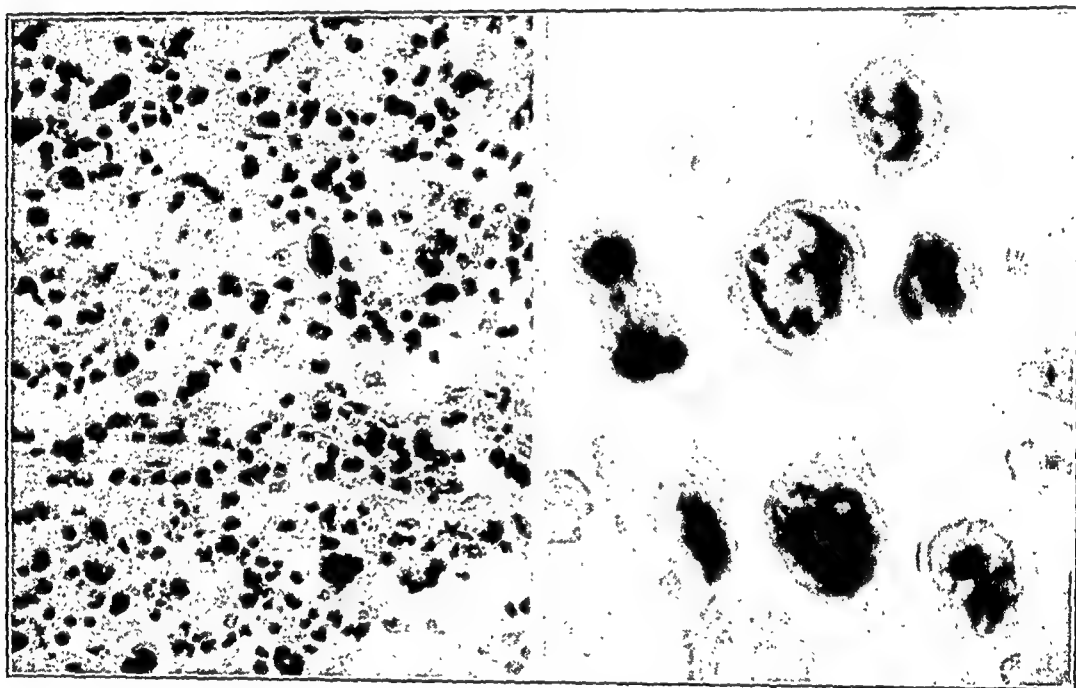


Fig. 3.

Fig. 4.

Fig. 3.—The polymorphism of the tumor, as it involves the epicardium of the right auricle, may be seen. Large cells with abundant cytoplasm, others with tendency to spindle formation, especially in the background, may be noted (hematoxylin and eosin, $\times 365$).

Fig. 4.—Mediastinal lymph node. Cells with abundant reticulated cytoplasm, and small cytoplasmic vacuoles (Mallory's phosphotungstic acid hematoxylin, $\times 1875$).

no evidence of tumor. The thyroid gland was atrophic, but otherwise revealed no lesions. The cervical nodes were not remarkable in any way. The esophagus, stomach and intestinal tract were normal. The pancreas was normal, except for one firm pinkish white nodule 0.5 cm. in diameter in the body of the gland. There was one metastatic nodule 1 cm. in diameter in the liver. The spleen was normal. The left suprarenal gland was enlarged and appeared to be diffusely involved by an infiltrative type of neoplastic process without loss of identifiable units of the gland. The right suprarenal gland was similar, but revealed only a small fragment of tumor. There were no metastatic growths in the kidneys. The left kidney was atrophic, and weighed 30 gm., apparently representing old, healed pyelonephritis. The right kidney was correspondingly enlarged, and weighed 200 gm.; it was essen-

tially normal. Except for left cystic pyelitis and ureteritis, the remainder of the urinary tract was normal. There were multiple, small, subserous leiomyomas in the uterus. The adnexa were normal. The brain was not examined.

Microscopic sections of the tumor, taken from the pericardium and myocardium, revealed a highly malignant neoplasm of polymorphous cell type. In the myocardium the tumor cells tended to invade the muscle-bundle interspaces, but occasionally large aggregations of tumor cells were formed, from which cardiac muscle cells had entirely disappeared. Both pericardium and epicardium were involved by the tumor, and the normal spaces between these structures were obliterated by tumor and organizing fibrinous exudate. The neoplastic cells were usually large and spherical or oval, with some tendency to long spindle shapes (Fig. 3). The smaller cells resembled lymphocytes, although they were somewhat larger. In these, there was usually a scant amount of cytoplasm. In the cells of greater size the cytoplasm was abundant, and had marked affinity for the eosin stain. The cytoplasm of the larger cells was sometimes foamy, due to small, unstained vacuoles (Fig. 4). In other cells a fine, reticular, cytoplasmic structure was identified. This sometimes, by use of Mallory's



Fig. 5.—*A*, Mediastinal lymph node. Giant cell with abundant cytoplasm and multiple nuclei. Faint longitudinal fibrillae and rows of evenly placed granules resembling embryonic sarcous elements or striations may also be seen faintly in the cytoplasm (Mallory's phosphotungstic acid hematoxylin, $\times 1250$). *B*, Biopsy revealed metastasis to deltoid muscle. Polymorphous character of cells with many oval or spindle forms may be noted (hematoxylin and eosin, $\times 250$).

phosphotungstic-acid hematoxylin stain, was revealed as very fine, scarcely visible longitudinal fibrillae, with more deeply stained granules in dotlike lines. These suggested concentration points of embryonal sarcous elements, the striations of embryonic muscle cells (Fig. 5*A*). Nuclei of the tumor cells were usually large, hyperchromatic structures, often with finely divided chromatin. This gave some nuclei the appearance of a meshwork of chromatin. Some cells had two or three large nuclei. Mitotic figures were fairly numerous. Cells were often undergoing retrogressive changes, and in these the nuclei were in a state of karyorrhexis. In several portions of the tumor necrosis was advanced. This was especially the case in the epicardium. Lymphocytes and polymorphonuclear neutrophilic leucocytes were collected in aggregations, particularly in the epicardium and pericardium, and at

the periphery of necrotic portions of the tumor. Vessels of the epicardium and myocardium were often surrounded by tumor cells, and some of them contained cells of similar appearance which packed their lumina. Metastatic involvement was proved to be present, by microscopic sections, in the right deltoid muscle (two specimens for biopsy; Fig. 5B), lungs, liver, suprarenal glands and lymph nodes (mediastinal, aortic and mesenteric). In all of these the morphological characteristics of the cells were either identical with or similar to those observed in the heart and pericardium. The extreme degrees of polymorphism which were disclosed by the tumor in the pericardium and myocardium were exhibited less frequently by the metastatic growths; however, marked variations in size, shape and staining of the cells did occur. The metastatic growths in the deltoid muscle, mediastinal lymph nodes, and lungs, as in portions of the cardiac tumor, revealed extreme degrees of necrosis; however, there were always areas of preserved cells near the periphery of the growth. In the aortic and mesenteric lymph nodes, and in the suprarenal glands, the tumor cells were evidently young and well preserved, and offered excellent opportunity for detailed study of individual cells. In all situations about the tumors, the blood vessels appeared to be invaded, and in sections elsewhere, such as in the preparations of the leiomyomas of the uterus, tumor cells were often seen packing the lumina of the vessels. The nodule described in the body of the pancreas proved to be an adenoma composed of cells derived from islands of Langerhans.

The anatomical diagnosis was rhabdomyosarcoma, primary in the heart, with metastatic involvement of the pericardium, right deltoid muscle, liver, lungs, suprarenal glands, and lymph nodes.

COMMENT

Electrocardiography.—The electrocardiographic findings in this case, in conjunction with the specimen of muscle removed for biopsy, furnished the key to the correct diagnosis. The sudden appearance of complete auriculoventricular dissociation when previous electrocardiograms had not indicated any disturbance of conduction, suggested that the malignant process which had invaded the deltoid muscle had also invaded the bundle of His. There was no way of knowing, during life, that the malignant process was primary in the heart.

The electrocardiogram in the case reported by Willius and Amberg, mentioned in the early part of this paper, revealed incomplete bundle-branch block of a type indicating involvement of the right bundle-branch (new terminology). This electrocardiographic change is entirely consistent with the fact that the only portion of the right ventricle that was not involved by the tumor was the right anterior portion of the conus. The RS-T changes present in the tracing could easily be explained by the conduction defect in the right bundle-branch.

Lloyd published the electrocardiogram in a case in which the P-R interval was 0.28 second. At necropsy, a tumor was found in the region of the auriculoventricular node. The electrocardiogram in a case reported by Houck and Bennett was essentially negative except for slight changes in the S-T interval, possibly caused by treatment with digitalis. The tumor in this case involved the left auricle.

In the electrocardiogram published by Siegel and Young, the T-waves were inverted in all leads, and the RS-T contours were convex in all leads. There was no evidence of defects of conduction in the tracing. One of us (Barnes) has seen an almost exact replica of this tracing develop a few weeks after occlusion of the anterior descending branch of the left coronary artery complicated by extensive pericarditis. It is interesting to note that Siegel and Young found that the tumor involved an area of the left ventricle, corresponding to that involved by infarction when the descending branch of the left coronary artery is occluded; but they also recorded invasion of the epicardium of the posterior surface of the heart by the tumor. This might correspond to the epicardial involvement observed in the case of coronary occlusion just cited as having been encountered by one of us. The epicardial involvement also might account for the close similarity of the tracings in the two cases. It is our belief that a tumor invading the left ventricle, that does not involve either bundle-branch if localized to the anterior apical or the posterior basal portion of that ventricle, would produce an electrocardiogram which is similar to that obtained in the stage of fibrosis subsequent to acute myocardial infarction. Elevation of the level of take-off of the RS-T segment would not be anticipated from tumorous invasion of the left ventricle, for the acute cellular and vascular reaction which follows acute myocardial infarction is lacking. Likewise, a changing RS-T segment, as seen in acute myocardial infarction, would not be expected in a tumor of the left ventricle, for these RS-T changes in acute infarction are associated with a rapidly changing cellular reaction. This point is well illustrated in the case reported by Siegel and Young.

On the basis of published tracings and on theoretical grounds, it is to be anticipated that most of the electrocardiographic changes that will be observed in cases of tumor of the heart will result from neoplastic invasion of the ventricles. It is probable that invasion of the conducting systems will account for a majority of abnormal electrocardiograms. Because of the much more frequent invasion by tumors of the right ventricle than of the left, right bundle-branch defects should exceed those of the left bundle-branch. Invasion of the muscle of the left ventricle without involvement of the bundle-branches or of the pericardium should produce tracings closely similar to those obtained in the fibrotic stage following acute myocardial infarction. Invasion of the epicardium, either alone or in conjunction with involvement of the ventricles, may produce or modify changes in the waves.^{3, 7} If a patient, known to have or to have had a neoplasm, more or less suddenly exhibits these electrocardiographic changes in the absence of any other pathological process in the heart to explain them, then they constitute important presumptive evidence that the malignant process has invaded the heart.

Pathology.—As we have stated previously, primary sarcoma of the heart is a pathological rarity. Perlstein, in 1918, by careful selection, admitted thirty cases of this condition from a compilation of the literature, and added an additional case. Lymburner recently (1933) reviewed the literature exhaustively, and was able to collect fifty-seven cases. Primary sarcomas of the heart have been designated as spindle-celled, giant cell, lymphosarcoma, round-celled sarcoma, mixed-cell sarcoma, fibrosarcoma or myxosarcoma, in agreement with the histological details presented by the cellular constituents of the tumors. Apparently the diagnosis of rhabdomyosarcoma has been made only once, this in a case reported by Bradley and Maxwell, in 1928.

Primary rhabdomyoma of the heart has been less often diagnosed, according to reports in the literature. Of this type of tumor, Lymburner could find only forty-seven examples, and added another case. Primary cardiac rhabdomyomas are considered to be benign tumors, in the sense that in none of the examples referred to in the literature have metastatic growths been noted, although they have been multiple in the heart. Rhabdomyomas predominate in the early years of life. Of the 48 cases collected by Lymburner, 20 occurred within the first year of life, and only 5 between the twentieth and forty-fifth years. Rhabdomyomas of the heart have a further distinctive characteristic in being associated frequently with functional or anatomical developmental defects, epilepsy and tuberous sclerosis of the brain being the two most common of many such disturbances which have been found. It is believed that rhabdomyomas are an expression of abnormal tissue differentiation, or represent secondary developments from embryonic tissue rests. They present a characteristic microscopic picture, in which the large, irregularly processed and vacuolated, so-called "spider cells," and long spindle cells with delicate longitudinal fibrillae and cross striae form the essential differential points. The cells frequently contain excess glycogen.

The relationship which the typical rhabdomyoma of the heart might bear to primary sarcoma of the heart is difficult or impossible to ascertain accurately, since only once has the differentiation in sarcoma been considered sufficient to admit the diagnosis, primary rhabdomyosarcoma. From a more or less superficial survey of the field, it would appear that the two types of tumor are distinct, and with possible exceptions, it seems improbable that primary sarcoma of the heart arises from malignant transformations of a rhabdomyoma. Transitional stages apparently do not exist, for as Lymburner remarked: "All reported cases (of rhabdomyoma) seemed to possess a similar microscopic appearance, regardless of the age of the patient, and evidently had obtained their final development in embryonic life." Primary sarcomas and rhabdomyomas of the heart are further distin-

guished in that they appear in different age groups. Although cardiac rhabdomyomas predominate among young people, cardiac sarcomas predominate among middle-aged and older people; only two cases have been recorded in which the patients were less than twenty years of age. Also, primary sarcomas are not associated with developmental defects, whereas rhabdomyomas usually are.

In reviewing cases reported in the literature, we have found that there was one which strikingly resembled the case reported here. The case was described by Bradley and Maxwell. Their patient was a man, aged sixty-two years; his clinical history was similar to that recorded for our patient. The gross and microscopic appearances of the tumor in each case were similar, although not identical. The histological differentiation of the tumor described by Bradley and Maxwell was as a polymorphous cell sarcoma with many long spindle cells revealing fibrillae and acidophilic cytoplasm. Sections of the tumor were submitted by Bradley and Maxwell to Mallory, Ewing and Broders. All concurred in the diagnosis of rhabdomyosarcoma.

We have concluded,* as Bradley and Maxwell did in their case, that the diagnosis of the tumor in our case should be rhabdomyosarcoma, primary in the heart. In proof of this we must necessarily first offer evidence that the tumor was of primary cardiac origin. As evidence we may cite the clinical history, which gave every indication that the patient's illness from beginning to end was cardiac. Further proof of the cardiac origin is offered by the macroscopic findings at necropsy. Relatively speaking, although metastasis had occurred, scarcely any tumor was found outside the heart and pericardium. The pericardium and epicardium were involved throughout, and the right auricle and right ventricle were extensively infiltrated. The metastatic areas were small and nowhere gave the impression of primary sarcoma. Conversely, the cardiac tumor had no resemblance to metastatic tumors of the heart, many examples of which we have seen. Microscopic examination gives additional evidence of the primary cardiac nature of the tumor, by way of its histological differentiation. The cells of the tumor were extremely polymorphous; there were many oval or long spindle forms; the larger cells had abundant acidophilic cytoplasm; in a few cells faint fibrillae and striations were observed. Because of the extreme degree of malignancy, the cells were usually totally undifferentiated. However, there were some, as indicated, which revealed sufficient detail to allow identification of the exceedingly suggestive fibrillae and striations. These could hardly be expected to be so clearly defined as in the slowly growing rhabdomyomas, because of the high degree of malignancy of the tumor. The summation of this evidence, we believe, warrants the conclusion, as previously stated.

*Dr. H. E. Robertson and Dr. A. C. Broders have reviewed the sections of this tumor and have concurred in the diagnosis of rhabdomyosarcoma.

SUMMARY

A case is presented in which a diagnosis of tumor of the heart was made during life. The electrocardiographic abnormalities that have been reported in cases of cardiac tumor are reviewed; in our case, the electrocardiographic changes observed were important in establishing the diagnosis. Careful study of the pathological changes in our case, we believe, permits the conclusion that the tumor was a rhabdomyosarcoma, primary in the heart.

REFERENCES

1. Adami, J. G., and Nichols, A. G.: *The Principles of Pathology*, Philadelphia, 1908-1909, p. 158, Lea & Febiger.
2. Armstrong, H., and Mönckeberg, J. G.: Herzblock, bedingt durch primären Herztumor, bei einem 5-jährigen Kind, *Deutsches Arch. f. klin. Med.* 102: 144, 1911.
3. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
4. Beck, C. S., and Thatcher, H. S.: Spindle Cell Sarcoma of the Heart, *Arch. Int. Med.* 36: 830, 1925.
5. Bradley, E. B., and Maxwell, E. S.: Primary Neoplasms of the Heart; Report of an Unusual Case, *J. A. M. A.* 91: 1352, 1928.
6. Diebold, Otto: Über das Primäre Herzsarkom, *Ztschr. f. Kreislaufforsch.* 22: 785, 1930.
7. Fowler, W. M., Rathe, H. W., and Smith, F. M.: The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *AM. HEART J.* 8: 370, 1933.
8. Goldstein, H. I.: Tumors of the Heart, *New York M. J.* 115: 97, 158, 1922.
9. Houck, G. H., and Bennett, G. A.: Polypoid Fibroma of the Left Auricle (So-Called Cardiac Myxoma) Causing a Ball-Valve Action, *AM. HEART J.* 5: 787, 1930.
10. Karrenstein: Ein Fall von Fibroelastomyxom des Herzens und Kasuistisches zur Frage der Herzgeschwülste, besonders des Myxome, *Virchow's Arch. f. path. Anat. u. Physiol.* 194: 127, 1908.
11. Lloyd, P. C.: Heart Block Due to Primary Lymphangio-endothelioma of Atrio-ventricular Node, *Bull. Johns Hopkins Hosp.* 44: 149, 1929.
12. Lymburner, R. M.: Tumors of the Heart; Histopathologic and Clinical Study, *Canad. M. A. J.* (In press).
13. Matras, A.: Ein Primäres Sarkom des Herzens, *Ztschr. f. Kreislaufforsch.* 19: 233, 1927.
14. Meroz, E.: A Clinical Study of Three Cases of Primary Tumor of the Heart, *Internat. Clin.* 4: 231, 1917.
15. Perlstein, J.: Sarcoma of the Heart, *Am. J. M. Sc.* 156: 214, 1918.
16. Pommer, G.: Zur Kenntnis der Primären Herzgeschwülste, *Ztschr. f. Kreislaufforschung.* 23: 65, 1931.
17. Siegel, M. L., and Young, Anna M.: Electrocardiographic Findings in Tumors of the Heart: With a Report of a Case, *AM. HEART J.* 8: 682, 1933.
18. Uehlinger, Erwin: Über einen Fall von diffusem Rhabdomyom des Herzens, *Virchow's Arch. f. path. Anat. u. Physiol.* 258: 719, 1925.
19. Willis, F. A., and Amberg, Samuel: Two Cases of Secondary Tumor of the Heart in Children in One of Which the Diagnosis Was Made During Life, *M. Clin. North America* 13: 1307, 1930.

RUPTURE OF NORMAL CHORDAE TENDINEAE OF THE MITRAL VALVE*

CHANNING FROTHINGHAM, M.D., AND GEORGE M. HASS, M.D.
BOSTON, MASS.

RUPTURE of one or more chordae tendineae of the heart may occur following infectious lesions in endocarditis or because of lesions of papillary muscles. These are the only responsible conditions recorded by White¹ and by Vaquez² in their comprehensive reviews of the literature. If rupture of chordae tendineae under other circumstances has been reported, diligent searchers have not brought it to light. It seems obligatory, therefore, to report a case, probably unique, of rupture of the chordae tendineae in which no disease of these structures or of the papillary muscles could be found. In this case there was calcification in a part of the mitral valve to which the ruptured chordae tendineae were attached. The possible relationship between this calcification and the rupture will be discussed later, but the chordae tendineae at the site of the rupture appeared to be normal.

CASE REPORT

The patient (Medical number 41737), was a man sixty-five years of age. He came to autopsy on April 9, 1933, having been ill in bed since the preceding August. The first weeks of his illness were spent at St. Luke's Hospital in New Bedford and the later months at the Peter Bent Brigham Hospital in Boston. So far as the present problem is concerned, his family history was unimportant. The following data are all that could be collected about his past cardiac history. He had rowed in college for four years on the varsity crew and it may be assumed that his heart was not remarkable during that period as there was then a physician who examined the athletes. When he was forty-six years old, an excellent physician made a note that his heart was "negative excepting for soft first sounds." When he was about sixty-three years of age, another excellent physician examined his heart and found no murmurs. For the year preceding his final illness he was reported as saying that he became somewhat short of breath on exertion so that he could not swim or row so far as formerly. He also said that he had had some cough for the past two years without apparent cause. Otherwise his past history was unimportant. He was a man of excellent habits, and he kept himself physically in good condition and did not become overweight. There was no history of syphilis, and the Wassermann reaction of the blood serum was negative.

His present illness began with an attack of shortness of breath which awakened him from sleep about two o'clock on the morning of August 7, 1932. On the afternoon before, he had rowed a boat for over an hour against wind and unfavorable tide. He did not overexert himself and experienced no dyspnea or weakness. After the row he went swimming and after that walked up a steep hill to his home. So

*From the Medical Service and Pathological Service of the Peter Bent Brigham Hospital, Boston.

far as can be ascertained he did not experience any discomfort during that evening and went to bed without suspicion of anything unusual in his physical condition. When seen by Dr. Russell Wood of New Bedford about three o'clock in the morning he was cyanotic and markedly dyspneic. He had pulmonary edema and tachycardia. Under morphine and atropine he improved rapidly and had several hours' sleep. The dyspnea with pronounced orthopnea continued. On August 12, 1932, he entered St. Luke's Hospital in New Bedford. At this time the physical examination in addition to the orthopnea and cardiac abnormalities showed a few scattered râles in the chest and slight edema of the ankles. The heart appeared somewhat enlarged to percussion. No thrills were felt. The first sound all over the precordia was replaced by a harsh systolic murmur. No diastolic murmurs were heard. The rhythm was normal and the rate slightly accelerated. The blood pressure was 135 systolic over 85 diastolic. What his blood pressure had been before this upset could not be ascertained. The routine clinical pathology was essentially negative. An electrocardiogram taken on August 24, after he had been taking digitalis is reported as showing "heart muscle weakness and digitalis effect." One of the authors (C. F.) saw him on August 26, at which time the conditions were practically the same as described above. The amount of dyspnea and orthopnea seemed out of proportion to the slight amount of edema of the legs and over the sacrum. Furthermore, the edema had been gradually increasing, so that it seemed reasonable to believe that some sudden injury to the heart had occurred, and in consequence cardiac decompensation was gradually developing. The possibility of a coronary occlusion without pain was seriously considered, although the unusually harsh systolic murmur could not be accounted for on this basis. Others thought that there had been gradually increasing myocardial weakness which had been suddenly accentuated by the strenuous day preceding the upset. When seen next by one of the authors (C. F.) on September 3, conditions were practically the same except that the edema of the legs and over the sacrum was more pronounced.

For the remainder of his stay at St. Luke's Hospital the evidence of cardiac decompensation increased slightly despite excellent cooperation on the patient's part and careful nursing. On September 21, he entered the Peter Bent Brigham Hospital, where he remained until his death from a terminal bronchopneumonia on April 9, 1933. The outstanding features of the case during his stay of over six months at the Brigham Hospital were the attempts to develop cardiac compensation and the gradually increasing psychosis. He was practically afebrile during his stay in the Brigham Hospital except for a few days in January and during the terminal infection. His pulse showed a regular rhythm and usually ranged between 80 and 90 beats per minute. Rarely it reached 110 beats per minute, and often it ranged between 70 and 80. Respirations were usually about 20 per minute. Occasionally they went up to 25 but often were about 15.

By the end of September the edema of the legs and over the sacrum had increased; ascites was present and hydrothorax existed on both sides. The liver was also easily palpable, three fingerbreadths below the right costal margin. Late in September Cheyne-Stokes breathing developed and continued until his death. He also began to be disoriented at night. Despite excellent responses to theocin and later salyrgan the dropsy could be only temporarily relieved and the liver remained enlarged. He gradually improved in regard to orthopnea so that he was able to lie back with only three pillows at times. However, it could not be said that his circulation ever became reestablished to normal. The systolic blood pressure during his six and one-half months' stay in the hospital ranged from 160 to 128 and the diastolic from 104 to 76. On January 19 a systolic thrill was felt over the base of the heart when the patient leaned forward, but this did not persist. No other murmurs ever developed and the systolic murmur remained the same.

The patient's mental condition during these six and one-half months ranged from normal to moderate disorientation and irrationality and then to almost active mania.

In the months of February and March he had a few convulsive attacks, the cause for which was not clear, followed by no sequelae. Because of a corneal scar only one eyeground was visible, but this appeared to be normal. In April he developed a bronchopneumonia to which he succumbed in a few days.

The autopsy was performed by one of the authors (G. H.) two and one-half hours after the patient's death. The anatomical diagnoses are as follows: *ruptured chordae tendineae of posterior mitral cusp (healed)*; *calcification of annulus fibrosus of mitral valve (posterior cusp)*; *cardiac dilatation*; *hydrothorax*; *ascites*; *chronic passive congestion of viscera*; *arteriosclerosis (slight, generalized)*; *bronchopneumonia (immediate cause of death)*; *pleuritis (serofibrinous)*; *hyalinization of islets of Langerhans*; *cirrhosis of liver*; *encephalomalacia (focal)*.

As the most important lesions were in the heart, the description of that will be given first.

Heart—Gross Appearance.—In the pericardial cavity there were 20 c.c. of clear fluid. The heart, as it lay in situ, was dilated. The right auricle and right ventricle were greatly distended. The left auricle was much less prominent than the right. The left ventricle was relatively contracted. The coronary arteries were neither unusually tortuous nor thick walled. The heart weighed 360 grams. The measurements of the circumference of three valvular orifices were as follows: tricuspid, 14 cm.; pulmonary, 8 cm.; and aortic, 7.5 cm. The cusps, chordae tendineae and papillary muscles of these valves were essentially normal.

The mitral valve and its annulus fibrosus, chordae tendineae and papillary muscles were the seat of the only significant pathological changes in the heart. The orifice easily admitted the passage of two fingers. When viewed from the auricular side, it was noted that the middle three-fifths of the posterior cusp bulged upward into the mitral opening. The valve ring was not disturbed, and the left ventricle was carefully opened by a lateral incision which was carried through the ventricular wall between the anterior and posterior groups of papillary muscles. As was suspected, the middle one-third of the posterior cusp was almost entirely free from its attachments to the papillary muscles. Four ruptured chordae tendineae were found. The distal portions were traced for distances of from 2 to 10 mm. to points where they branched into fibrous cords, which were attached either to the free margin or to the ventricular surface of the middle one-third of the posterior cusp. The proximal portions of the four ruptured chordae were from 2 to 10 mm. in length. Three were attached to the posterior group of papillary muscles and one to the anterior group. The free ends were tapered smooth and rounded. The remnants of the chordae were slightly contracted and atrophic. There were no apparent gross defects in the structure of either the chordae which had ruptured or those which had preserved their usual continuity. Except for slight atrophy of the musculature adjacent to the attachment of the ruptured chordae tendineae, the papillary muscles were normal. Although there was slight bluntness of the free margin of the middle portion of the posterior cusp, the cusps of the mitral valve were essentially normal. There was no evidence of either a healed or active endocarditis involving the valve leaflets or chordae tendineae. However, in the annulus fibrosus there were irregular masses of calcium which extended for from 1 to 3 mm. into the substance of the valve at its attachment. Of greatest significance was the restriction of these calcific deposits to the annulus fibrosis of the posterior cusp, especially at the attachment of that portion of the leaflet which was affected by the rupture of the chordae tendineae.

The musculature of the left ventricle was from 15 to 17 mm. in thickness and that of the right ventricle 4 mm. Numerous incisions disclosed no pathological

changes. The orifices and lumina of the coronary arteries were not narrowed. Only a few slightly elevated atheromatous plaques were encountered in the intima of these vessels.

Heart—Microscopic Study.—The individual muscle fibers showed no degenerative changes and there were no cicatrices. The walls of scattered arterioles were slightly thickened and hyalinized. The intima of the medium-sized coronary arteries was slightly thicker than normal.

Chordae Tendineae: Serial sections were made through three of the ruptured chordae and several of the adjacent intact chordae tendineae. It was concluded after



Fig. 1.—Photograph illustrating ruptured chordae tendineae of posterior cusp of mitral valve and the irregularity at the attachment of the cusp produced by calcification in the annulus fibrosus.

a histological study of the former that the duration of time since the rupture had been sufficient to permit repair of the broken ends. In the tissue adjacent to the points at which the chordae tendineae parted there was no inflammatory reaction or apparent preexisting defect in the structure. Neither were there vegetations. The tissue was composed of dense as well as loose-textured avascular collagen in which stellate and fusiform connective tissue cells were imbedded. Covering the surface of each chorda, even at the point of separation, there was a layer of endothelial cells. The histology of the intact chordae, which were cut in serial sections for the purpose of making control studies, differed from that of the ruptured chordae

tendineae in that the collagen fibrils were arranged in normal, compact, straight, parallel bundles which were of uniform texture.

Papillary Muscles: Sections through the papillary muscles at the origins of the ruptured chordae tendineae were essentially negative except for slight atrophy of the muscle fibers.

Other Organs—Gross Appearance.—The remaining organs on gross inspection showed a few changes worthy of mention. There was evidence of congestion, edema and bronchopneumonia in each lung. In the right pleural cavity there were 1,050 c.c. and in the left 450 c.c. of slightly turbid fluid, which contained a few flakes of fibrin; 100 c.c. of clear watery fluid were found in the peritoneal cavity. The liver weighed 1,870 grams and had a slightly thickened irregular capsule. The parenchyma had the typical mottled appearance of a "nutmeg" liver and a mild cirrhosis, both of which were the result of chronic passive congestion. The spleen weighed 220 grams. There was moderate engorgement but no increase in the amount of stroma.

The right kidney weighed 200 grams and the left kidney 180 grams. The cortical substance measured from 5 to 6 mm. in thickness, and except for small scattered subcapsular scars, the parenchyma of each organ was normal. The pancreas, adrenals, thyroid, prostate and pituitary were normal. The aorta retained much of its elasticity, and there was only slight atherosclerosis. A study of the brain revealed large pacchionian granulations, slight fibrous thickening of the pia-arachnoid, and a small area of softening (2 mm. \times 3 mm.) in the left globus pallidus. The lumen of the left lateral sinus was very small.

Microscopic Study of Other Organs.—**Lungs:** The principal variations from normal histology may be attributed to chronic passive congestion and an acute bronchopneumonia. In many alveolar spaces there were aggregates of mononuclear leucocytes. The majority of these were heavily laden with hemosiderin. The inter-alveolar septums were doubled in thickness. This was due, not only to distention of capillaries, but also to edema and fibrosis of the stroma. Although an increase in the amount of collagen was most prominent in the alveolar walls, it was also apparent elsewhere, especially in the stroma which supported small and medium-sized blood vessels. This contributed in part to the increased thickness of the walls of veins and arteries. This thickening was due not only to the presence of an unusual amount of collagen in the adventitia, but also to a deposition of similar material in the media and intima. This was especially prominent in the walls of arteries, for in these vessels the intima was thickened, and the smooth muscle was scanty or fragmented. An exudate composed largely of fibrin and polymorphonuclear leucocytes in several alveolar spaces and respiratory passages was the only other significant finding.

Liver: There were moderate changes which were the result of chronic passive congestion. The central veins, the sinusoidal channels and especially the veins in the portal areas were engorged. There was an increase in connective tissue, principally in the portion of the liver which was adjacent to the capsule. The fibrosis was present not only around central veins and adjacent sinusoids but also around the portal structures. The cytoplasm of a few liver cells contained vacuoles which were indicative of a slight degree of fatty metamorphosis.

Spleen: There was moderate hyperplastic sclerosis of the arterioles, dilatation of the sinusoidal spaces, and a slight increase in the amount of connective tissue in the trabecula and between the sinusoids.

Kidneys: The pathological features were not of importance. Hyaline thickening of capillary loops of glomeruli and hyperplastic sclerosis of arterioles were found in the small scattered radial subcapsular cicatrices. These mild changes were considered to be of arteriosclerotic origin.

Pancreas: There was a prominent accumulation of pale, homogeneous or slightly granular, acidophilic hyaline material beneath the endothelium of the capillaries of the islets of Langerhans. Although the distribution of this substance was relatively uniform, in many islets it was of sufficient amount to obliterate the alpha and beta cells. Occasional arterioles showed slight mural hyalinization.

Adrenals: The adrenal cortex and medulla were negative. In the periadrenal tissues there was atrophy of fat, edema of fibro-adipose tissue, and moderate hyperplastic sclerosis of arterioles.

Thyroid: The histology was that of a normal gland.

Prostate: A slight hyperplasia with chronic prostatitis and attendant fibrosis constituted the only findings.

Pituitary: The pars anterior was negative. In the pars intermedia there was a pale, homogeneous or slightly granular material which was located in the walls of capillaries. This deposit closely resembled that which was described in the islets of the pancreas. Small clusters of basophilic cells were found in the pars nervosa adjacent to the pars intermedia.

Aorta: There were very slight variations from normal histology. The fibrils of the intima were increased in number and thickness. Occasionally they were hyalinized, fragmented, and replaced by minute deposits of lipid.

Brain: Except for a slight increase in the amount of connective tissue of the pia-arachnoid and scattered minute lesions of arteriosclerotic origin, the brain was negative. The increase in collagen in the leptomeninges was no greater than that which is common in individuals of advanced age. Around blood vessels in the cerebrum, just beneath the gray matter of the cortex, there were occasional accumulations of lymphocytes and mononuclear leucocytes. In the latter there were yellow masses of pigment, which, inasmuch as it did not give the iron reaction, was considered to be a lipochrome pigment. In the globus pallidus there was an area of encephalomalacia (2 mm. \times 3 mm.). This was characterized by local sclerosis of arteries, degeneration of neural elements, gliosis and accumulations of vacuolated macrophages.

DISCUSSION

The lesions in the brain found at autopsy seemed hardly sufficient to cause the patient's mental disturbance, and it seems fair to say that this was a psychosis due to cardiac decompensation. The cirrhotic changes in the liver were presumably associated with the continued passive congestion. The histology of the lesions in the lungs due to passive congestion was of interest because in this case the events determined the duration of the passive congestion.

The fact that the weight of the heart was within normal limits shows that no appreciable hypertrophy could have existed before the sudden onset of his symptoms, especially as there had been time for some hypertrophy during the long final illness. This fact taken together with the report on the appearance of the myocardium justifies the assumption that the heart was in a satisfactory condition before

the onset of acute symptoms. The strenuous activity which he carried out on the day before the onset of his illness also supports the view that the heart was in good condition and that the slight symptoms of circulatory disturbance which have been mentioned in his past history were of no practical importance. The weight of the heart also justifies the assumption that he did not have an elevated blood pressure previous to his final illness that had persisted long enough to affect his heart. Therefore it seems reasonable to consider that the onset of the cardiac symptoms was associated with the rupture of the chordae tendineae and the subsequent incompetency of the mitral valve. The systolic murmur must have been caused by this incompetency. What little evidence there is points to its absence before his last illness. It is impossible to decide just when the chordae tendineae ruptured, but speculation on this point is interesting. It would be natural for them to rupture during exertion, since the rupture seemed to be purely a mechanical one and not dependent upon disease of the bands. Yet in view of the pronounced cardiac symptoms which developed rapidly and persisted, it would seem as though the onset of the symptoms must have been intimately associated in time with the development of the incompetency of the mitral valve. If such was the case, this incompetency must have developed during sleep and the rupture of the chordae occurred then rather than during the exertions of the afternoon before. Possibly some of the chordae might have ruptured during the exertions of the afternoon and the rupture of the ones which caused the incompetency of the mitral valve happened later from the unusual strain imposed upon them by the rupture of one or more during the exertion.

The histological study shows that there was no acute disease of the ruptured chordae and that except for the rupture and subsequent contraction and atrophy they appeared normal. It also showed that the papillary muscles to which they were attached were not diseased. Apparently, therefore, the rupture was purely a mechanical one, and it hardly seems that a congenital defect would be a factor in a man sixty-four years of age. As described above, in the leaflet of the mitral valve to which the ruptured chordae were attached there was a calcified area at the base, and it seems only reasonable to assume that this calcification may have been a factor in the mechanics which caused the rupture. Up to now, however, reports of rupture of normal chordae tendineae which are attached to diseased, distorted or calcified valves have not been found, and one might take the attitude that this calcification was not a factor in the rupture in this case. Whether or not it was a factor, the unique condition existed of a rupture of several normal chordae tendineae attached to one cusp of the mitral valve with resulting incompetency of the mitral valve. This patient's heart

was unable to adjust itself to the lesion so that a satisfactory circulation could be reestablished. It is interesting to note that prolonged cardiac decompensation can result in pure dilatation of the heart without increase in weight suggesting hypertrophy.

REFERENCES

1. White: Heart Disease, New York, 1931, The Macmillan Company.
2. Vaquez: Translated by Laidlaw, Diseases of the Heart, Philadelphia, 1924, W. B. Saunders Co.

OBSERVATIONS ON THE DURATION OF THE PHASES OF DIASTOLE IN MAN¹

ANNE BOHNING, M.D., AND JULIAN PLATT, M.D.
CHICAGO, ILL.

RECENTLY, on the basis of pressure curves recorded by optical methods in the various chambers of the heart and in large vessels, Wiggers^{2, 3} has shown that the diastole of the heart can be subdivided into a number of phases: (a) the period of *protodiastole*, during which the semilunar valves are closing; (b) the *isometric relaxation phase*, during which the heart is relaxing without change in its chamber volume, the valves being closed; (c) the period of *rapid inflow* following the opening of the A-V valves during which the relaxing heart fills rapidly from the auricles; (d) the period of *diastasis*, during which the ventricle fills more slowly; and finally, (e) the period of *auricular systole* in which the auricles contribute to the filling of the heart as it is activated. In his studies Wiggers^{2, 3} was able to define the durations of these phases in dogs, and in his laboratory Burstein⁴ was able to establish the durations in man. Aside from some scattered observations on auricular systole, there are no further data dealing with this subject. An attempt was made in the present investigation to determine the duration of these phases in man with normal and abnormal hearts. It was felt that such a study might contribute to an evaluation of the disturbances in dynamics which various types of heart disease might cause. In man it is difficult to arrive at the nature of the filling process in any other way. It was thought that a correlation of such measurements with the dynamic changes established by study in acute animal experiments might permit the transference of data derived from animal experiments more directly to man.

PROCEDURE

In the present study 15 normal subjects and 35 patients with various types of heart disease were studied. These patients with abnormal hearts were divided into the following groups: (a) those in which *mitral stenosis* was the predominant lesion and in which there was a sinus rhythm; (b) those in which *aortic regurgitation* was the predominant lesion and in which there was a sinus rhythm; (c) those in which

¹From the Heart Station and Cardiovascular Laboratory of the Department of Physiology, Michael Reese Hospital, Chicago.

²Aided by the Frederick K. Babson Fund and the Emil and Fanny Wedeles Fund for the Study and Investigation of Diseases of the Heart and Circulation, of the Michael Reese Hospital.

there was a combination of these two lesions and a sinus rhythm; (d) those with *myocardial damage* and sinus rhythm but no definite valvular disease; and (e) those with *auricular fibrillation* regardless of other cardiac involvement. Two cases of Group b were shown to be uncomplicated aortic regurgitation at autopsy.

All the subjects were brought to the heart station and placed in a prone or semiprone position. Simultaneous subclavian arterial and venous pulse tracings were obtained, usually with Lead II of the electrocardiogram. In some cases heart sounds were also recorded. The records were taken on film, using Wiggers' modification of the Frank

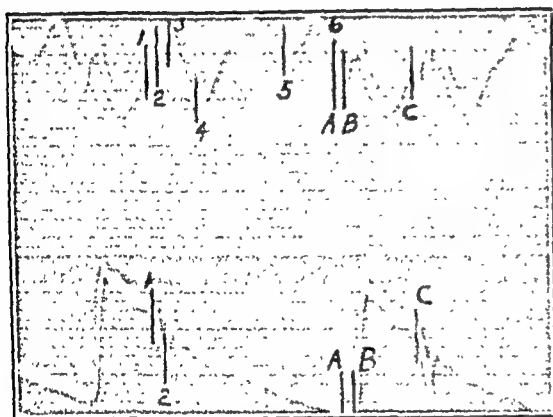


Fig. 1.

Fig. 1.—Simultaneous records of the pulses in the subclavian vein (upper) and artery (lower) showing the points used to define the different phases of systole and diastole. A to B, isometric contraction phase; B to C, systolic ejection phase; 1 to 2, protodiastole; 2 to 3, isometric relaxation phase; 3 to 4, rapid inflow phase; 4 to 5, diastasis; 5 to 6, auricular systole.

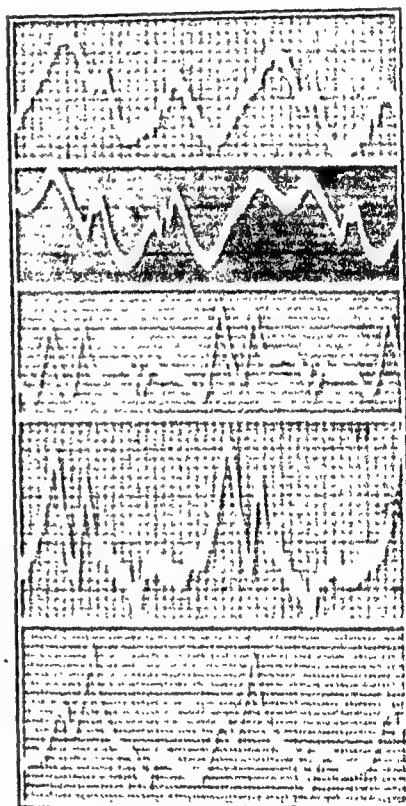


Fig. 2.

Fig. 2.—Five samples of subclavian venous pulses showing some of its typical forms.

segment capsule² and the double-slit lamp of Katz and Baker,⁴ with a point-o-lite bulb as a light source. Care was taken to avoid parallax (cf. Katz and Baker⁴). The patient held his breath while the record was taken in order to avoid distortion which might be produced by movement of the neck accompanying breathing. The other precautions utilized by Wiggers² were followed in taking these records. No attempt was made to quantitate the amplitude of the deflection which depends in these records on the degree of pressure applied on the

tambour, on the sensitivity of the recording system, on the proximity of the blood vessels to the tambour and on other factors. This inability to quantitate the amplitude did not interfere with the measurements of phasic durations. The procedure used in measuring the durations was similar to that established by Wiggers and employed by Burstein; it is shown in Fig. 1. It will be seen that the diastolic phases are measured primarily from the venous pulse and therefore give the duration of events in the right heart, the only exceptions being: (1) that protodiastole which is determined by the subelavian arterial pulse is a left-sided event; and (2) that the beginning of ventricular systole, and therefore the end of auricular systole, is determined by the left ventricle. Since Katz² has shown that the beginning and end of systole are not synchronous in the two ventricles, an unavoidable error is introduced in the determination of the phases of auricular systole and isometric relaxation of the right heart. The durations of the systolic phases which are measured from the arterial pulse are those of the left ventricle. We have found, in agreement with Wiggers,² that the contour of the subelavian venous pulse is variable, particularly in the variations introduced by the "systolic impact wave." In Fig. 2 are shown a few examples of the variability in contour encountered. With a little practice, however, and by correlating the venous pulse with the arterial pulse, no difficulty is encountered in defining the various diastolic phases. Only those records were used in this study in which the various phases could be clearly identified. The measurements could be made with an error of ± 0.01 sec.

RESULTS

A total of approximately 1,750 heart cycles were analyzed, using from 8 to 50 beats in each patient. The data thus obtained were handled in two ways: In the first place, the possible effect of cycle length on the different phases of diastole in the various types of cases studied was determined by charting the phase/cycle ratio as shown in Fig. 3, in which the ordinates give the duration of the phases in seconds and the abscissae the duration of the cycle length in seconds for each group of cases. In this way the effect of the lesion itself could be distinguished from the effect of cycle length. In order correctly to correlate the duration of these phases with the length of the heart cycle, the latter was measured from the beginning of one incisura to the next. This, the work of Wiggers and Katz has shown, is the proper way of analyzing the effect of heart rate on the phases of the cardiac cycle.

In the second place, a summary table, Table I, was made showing the extreme and predominant ranges and the commonest duration of each of these phases in the various types of heart diseases. To facilitate comparisons the measurements in the range of cycle length of

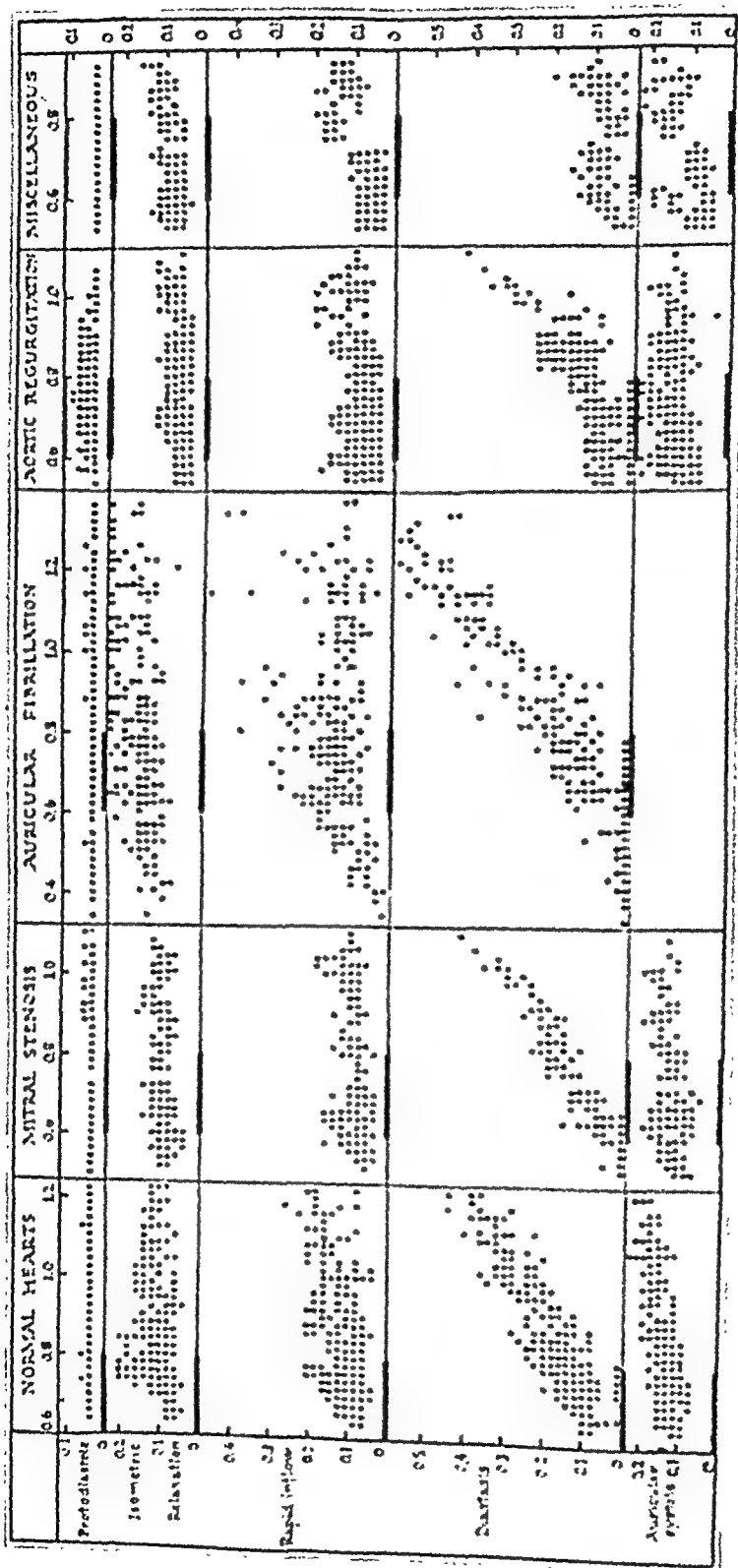


Fig. 2.—The dots represent the phase-to-phase relationship in the individual hearts assembled in groups 1-24, the normal hearts, mitral stenosis, auricular fibrillation, aortic regurgitation, and miscellaneous. (See the description in text.) The phase-to-phase cycle length in seconds is indicated by the dots. The dots are plotted on the line 0.6 to 1.0 of a second. For comparison the cycle length of 0.6 to 1.0 of a second is blocked out on the line 0.6 to 1.0 of a second.

from 0.7 to 0.8 second were selected, and the duration of the various phases in this cycle length range assembled in another summary table, Table II. A similar comparison can be made in Fig. 3 where cycle lengths from 0.6 to 0.8 second are indicated by blocks on the hori-

TABLE I

PATHOLOGICAL HEARTS									
NORMAL HEARTS	MITRAL STENOSIS	AURICULAR FIBRILLATION	AORTIC REGURGITATION				UNCOM- PLICATED	MIS- CELLANEOUS	
			COMPLICATED BY MITRAL LESION		OF ADVANCED DEGREE	SECONDS			
			OF MODERATE DEGREE	SECONDS					
									DEGREE
386	333	355	215	222	42	192			
15	9	6	6	4	2	8			
SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS			
0.04-0.06	0.04-0.06	0.04-0.06	0.04-0.06	0.04-0.08	0.04-0.10	0.04			
0.04	0.04	0.04	0.04	0.06-0.08	0.04-0.08	0.04			
0.04	0.04	0.06-0.30	0.04-0.12	0.06	0.04	0.04			
0.04-0.20	0.04-0.16	0.12-0.16	0.06-0.10	0.04-0.10	0.04-0.12	0.04-0.16			
0.08-0.14	0.08-0.12	0.12-0.16	0.06-0.08	0.04-0.08	0.08-0.10	0.08-0.12			
0.08-0.12	0.08-0.12	0.12-0.16	0.06-0.08	0.04-0.08	0.10	0.08-0.12			
0.04-0.26	0.04-0.18	0.00-0.46	0.04-0.18	0.04-0.20	0.04-0.14	0.04-0.20			
0.08-0.16	0.08-0.10	0.12-0.16	0.06-0.12	0.06-0.12	0.08-0.10	0.06-0.10			
0.08-0.16	0.08	0.12-0.16	0.08-0.10	0.08-0.10	0.08	0.08-0.10			
0.00-0.44	0.00-0.42	0.00-1.38	0.00-0.42	0.00-0.24	0.00-0.08	0.00-0.20			
0.08-0.28	0.00-0.22	0.00-0.20	0.08-0.24	0.08-0.16	0.00-0.08	0.08-0.12			
0.08-0.24	0.08-0.20	0.00-0.20	0.08-0.16	0.08-0.16	0.00-0.08	0.08-0.10			
0.08-0.24	0.06-0.20		0.08-0.20	0.08-0.22	0.12-0.22	0.06-0.24			
0.12-0.18	0.12-0.16		0.12-0.14	0.12-0.18	0.14-0.16	0.08-0.16			
0.12-0.16	0.12-0.16		0.12-0.14	0.12-0.16	0.14-0.16	0.10-0.16			
Protodiastole	Complete range								
	Predominant range								
	Commonest duration								
Isometric	Complete range								
Relaxation	Predominant range								
	Commonest duration								
Rapid Inflow	Complete range								
	Predominant range								
	Commonest duration								
Diastasis	Complete range								
	Predominant range								
	Commonest duration								
Auricular Systole	Complete range								
	Predominant range								
	Commonest duration								

TABLE I—CONT'D

PATHOLOGICAL HEARTS									
	NORMAL HEARTS	MITRAL STENOSIS	AURICULAR FIBRILLATION	AORTIC REGURGITATION				MIS- CELLANEOUS	
				COMPLICATED BY MITRAL LESION		UNCOM- PLICATED			
				OF MODERATE DEGREE	OF ADVANCED DEGREE				
No. of cycles estimated	386	333	355	215	222	42	192		
No. of individuals	15	9	6	6	4	2	8		
SYSTOLIC PHASES		SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS		
Isometric	0.04-0.06	0.02-0.06	0.04-0.10	0.04-0.08	0.04-0.08	0.04-0.10	0.02-0.10		
Contraction	0.04	0.04	0.04-0.08	0.04	0.04-0.06	0.04-0.08	0.04-0.08		
Complete range	0.04	0.04	0.04-0.08	0.04	0.04-0.06	0.04-0.08	0.04		
Commonest duration	0.20-0.34	0.16-0.30	0.08-0.32	0.16-0.30	0.14-0.34	0.18-0.28	0.16-0.36		
Systolic	0.24-0.28	0.18-0.26	0.18-0.24	0.18-0.28	0.24-0.28	0.22-0.24	0.20-0.28		
Ejection	0.26	0.18-0.26	0.22-0.24	0.26-0.30	0.24-0.28	0.22-0.24	0.20		
TOTAL DIASTOLE		SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS		
Complete range	0.38-0.90	0.26-0.74	0.18-1.74	0.32-0.74	0.32-0.62	0.36-0.46	0.28-0.62		
Predominant range	0.44-0.56	0.32-0.48	0.26-0.64	0.38-0.56	0.48-0.56	0.38-0.44	0.40-0.56		
Commonest duration	0.48-0.52	0.44	0.28-0.40	0.52-0.56	0.52	0.40	0.52		
TOTAL SYSTOLE		SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS		
Complete range	0.24-0.38	0.20-0.36	0.16-0.40	0.20-0.36	0.20-0.42	0.26-0.36	0.20-0.38		
Predominant range	0.28-0.32	0.24-0.28	0.20-0.32	0.30-0.34	0.28-0.32	0.26-0.30	0.24-0.32		
Commonest duration	0.30-0.32	0.24-0.28	0.24-0.32	0.30-0.34	0.32	0.30	0.24-0.26		
TOTAL CYCLE		SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS		
Complete range	0.64-1.22	0.48-1.06	0.34-2.06	0.54-1.06	0.56-1.00	0.64-0.76	0.52-0.92		
Predominant range	0.72-0.82	0.64-0.72	0.52-0.88	0.84-0.92	0.80-0.88	0.70-0.74	0.70-0.86		
Commonest duration	0.76	0.64	0.52-0.88	0.88	0.84-0.88	0.70	0.70		

TABLE II
DURATION OF PHASES OF CARDIAC CYCLE WHEN CYCLE LENGTH IS 0.70 TO 0.80 SECOND IN DURATION

PATHOLOGICAL HEARTS									
	NORMAL HEARTS	MITRAL STENOSIS	AURICULAR FIBRILLATION	AORTIC REGURGITATION				MIS- CELLANEOUS	
				COMPLICATED BY MITRAL LESION		UNCOM- PLICATED			
				OF MODERATE DEGREE	OF ADVANCED DEGREE				
DIASTOLIC PHASES	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS	SECONDS
Protodiastole	0.04-0.06	0.04	0.04	0.04-0.06	0.04-0.08	0.04-0.10	0.04-0.10	0.04	
Isometric	0.04	0.04	0.04	0.04-0.06	0.06	0.06-0.08	0.06-0.08	0.04	
Relaxation	0.04-0.20	0.08-0.12	0.10-0.22	0.08-0.10	0.04-0.08	0.04-0.12	0.04-0.12	0.06-0.12	
Rapid Inflow	0.08-0.16	0.10	0.14-0.16	0.10	0.06	0.08-0.10	0.08-0.10	0.06-0.12	
	0.04-0.20	0.04-0.14	0.08-0.38	0.06-0.16	0.04-0.14	0.04-0.14	0.04-0.14	0.04-0.18	
	0.06-0.12	0.06-0.08	0.12-0.20	0.06-0.12	0.06-0.10	0.04-0.08	0.04-0.08	0.06-0.16	
Diastasis	0.00-0.22	0.00-0.20	0.00-0.24	0.00-0.16	0.00-0.16	0.00-0.08	0.00-0.08	0.04-0.10	
	0.08-0.20	0.12-0.20	0.16-0.20	0.08-0.10	0.08-0.12	0.04-0.08	0.04-0.08	0.06-0.08	
Auricular	0.08-0.18	0.06-0.16		0.10-0.14	0.12-0.22	0.12-0.22	0.12-0.22	0.08-0.20	
Systole	0.12-0.16	0.12-0.16		0.12	0.12-0.20	0.14-0.20	0.14-0.20	0.10-0.18	
SYSTOLIC PHASES									
Isometric	0.04-0.06	0.04	0.04-0.08	0.04	0.04-0.08	0.04-0.10	0.04-0.10	0.04-0.06	
Contraction	0.04	0.04	0.04-0.08	0.04	0.04-0.04	0.08	0.08	0.04	
Systolic	0.20-0.28	0.22-0.26	0.14-0.24	0.24-0.28	0.20-0.28	0.18-0.28	0.18-0.28	0.16-0.28	
Ejection	0.22-0.26	0.22-0.26	0.18-0.20	0.26-0.28	0.22-0.28	0.22-0.28	0.22-0.28	0.18-0.24	
TOTAL DIASTOLE									
	0.40-0.54	0.42-0.52	0.44-0.56	0.40-0.52	0.40-0.52	0.36-0.46	0.36-0.46	0.40-0.56	
	0.44-0.52	0.42-0.48	0.46-0.54	0.40-0.52	0.44-0.48	0.40-0.44	0.40-0.44	0.42-0.54	
TOTAL SYSTOLE									
	0.24-0.32	0.22-0.30	0.22-0.28	0.28-0.32	0.24-0.38	0.26-0.36	0.26-0.36	0.24-0.32	
	0.26-0.30	0.24-0.28	0.22-0.28	0.28-0.30	0.28-0.32	0.28-0.32	0.28-0.32	0.24-0.28	

zontal lines separating the different phases in each group of cases.

A comparison was also made of the relation of the durations of the entire ventricular systole and the entire diastole to cycle length in each type of case. The results are assembled in Fig. 4, in which the lines represent means of the plotted points in each type of case represented.

DISCUSSION

An analysis of these tables and charts led us to the following summary of results:

Protodiastole was remarkably constant in duration and did not vary with cycle length. It was within the normal limits in most of the pathological conditions encountered. However, the cases with aortic

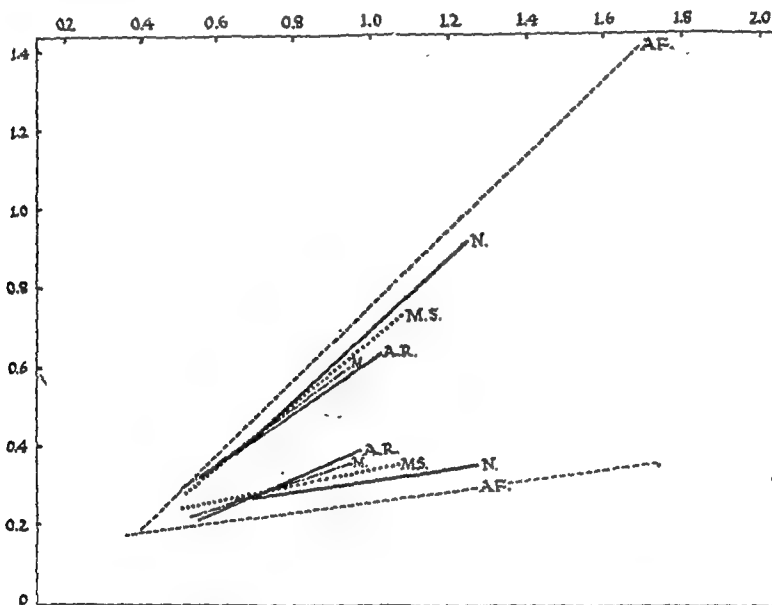


Fig. 4.—The lines represent the relation of the mean values of total ventricular systole (lower curves) and total ventricular diastole (upper curves) to cycle length. Abscissae represent cycle length in seconds—ordinates, the duration of systole and diastole in seconds. *N* is the mean of the group of normal hearts; *M.S.*, that of the group with mitral stenosis; *A.R.*, the group with aortic regurgitation; *A.F.*, the group with auricular fibrillation; and *M*, the miscellaneous group. (See the classification in text.)

regurgitation, uncomplicated or complicated, showed a conspicuous lengthening of this phase.

The isometric relaxation phase was not greatly influenced by cycle length. The variation in the duration of this phase was greater than normal in cases of auricular fibrillation, a variation which was apparently not dependent upon cycle length. It was consistently shortened in cases of aortic regurgitation.

The rapid inflow phase did not vary with cycle length. Its duration was relatively shorter than normal in all the pathological types of cases except in auricular fibrillation. In auricular fibrillation the scatter of individual determinations was more marked than in normal cases.

Diastasis was the one phase which varied directly with cycle length in every group of cases. This is brought out most clearly in the group of cases of auricular fibrillation where the greatest variation in cycle length was encountered. Some of these patients were digitalized, which may account for the extremely long diastolic phases found. However, the scatter was greater in auricular fibrillation than in the normals. In the other types of pathological cases the duration of diastasis was relatively shorter than normal.

Auricular systole showed no variation with cycle length. It tended to be longer than normal in the aortic regurgitation cases. Obviously, this phase was absent in cases of auricular fibrillation.

As had been already established by previous workers, both the total systole and the total diastole vary with the cycle length, the former showing less change than the latter. Except for auricular fibrillation it was found that the duration of systole was longer and the duration of diastole shorter in the abnormal cases than in the normal at the same cycle lengths. The auricular fibrillation cases, however, in confirmation of the observations of Katz and Feil,⁷ showed a total systole shorter than normal and a lengthened total diastole (longer than normal at the same cycle length).

TABLE III
COMPARATIVE TABLE OF PHASE DURATIONS IN NORMAL HEARTS

		OUR FINDINGS 15 CASES 386 CYCLES	FINDINGS OF WIGGERS AND ASSOCIATES
DIASTOLIC PHASES		SECONDS	(BURSTEIN) SECONDS
Protodiastole	Complete range	0.04-0.06	0.016-0.060
	Predominant range	0.04	0.030-0.050
	Commonest duration	0.04	0.038
Isometric Relaxation	Complete range	0.04-0.20	0.037-0.130
	Predominant range	0.08-0.14	0.060-0.090
	Commonest duration	0.08-0.12	0.076
Rapid Inflow	Complete range	0.04-0.26	0.055-0.173
	Predominant range	0.08-0.16	0.090-0.130
	Commonest duration	0.08-0.16	0.113
Diastasis	Complete range	0.00-0.44	0.080-0.708
	Predominant range	0.08-0.28	(Wiggers)
	Commonest duration	0.08-0.24	0.163
Auricular Systole	Complete range	0.08-0.24	
	Predominant range	0.12-0.18	(Wiggers)
	Commonest duration	0.12-0.16	0.110

In general our findings on the duration of the diastolic phases in normal cases agree fairly well with those given by Wiggers and by Burstein for man, as the comparison summarized in Table III will show. They, however, have reported averages, while we have reported the range of commonest durations; hence our durations for the various phases tend to be somewhat longer than those they give.

SUMMARY

We have measured the duration of each of the separate phases in approximately 1,750 cardiac cycles in 50 subjects, 15 of whom had normal hearts, the remaining 35 having some type of cardiac lesion. The diastolic phase durations in these different types of lesion have been tabulated and analyzed. These findings may be summarized as follows:

1. In auricular fibrillation total systole was found to be definitely shorter and total diastole definitely longer than in normal cases at the same cycle lengths. In all the other pathological types total systole was longer and total diastole shorter than in normal cases at the same cycle lengths.

2. In digitalized cases of auricular fibrillation the isometric relaxation and the rapid inflow phases tended to be prolonged.

3. In aortic regurgitation, protodiastole tended to be prolonged, isometric relaxation to be shortened, and auricular systole to be slightly prolonged in comparison to the duration of these phases in normal hearts.

We are grateful to Dr. Louis N. Katz at whose suggestion and under whose guidance this research was undertaken, for his advice and criticism.

REFERENCES

1. Wiggers, C. J.: Studies on the Consecutive Phases of the Cardiac Cycle. I. The Duration of the Consecutive Phases of the Cardiac Cycle and the Criteria for Their Precise Determination, *Am. J. Physiol.* 56: 415, 1921.
2. Idem: The Pressure Pulses in the Cardiovascular System, New York, 1928, Longmans, Green and Company.
3. Burstein, J.: The Diastolic Phases of the Cardiac Cycle in Man, *Am. J. Physiol.* 65: 158, 1923.
4. Katz, L. N., and Baker, W. R.: An Adjustable Double-Slit Lamp for Use in Multiple Optical Registrations, *J. Lab. & Clin. Med.* 10: 47, 1924.
5. Katz, L. N.: The Asynchronism of Right and Left Ventricular Contraction and the Independent Variations in Their Duration, *Am. J. Physiol.* 72: 655, 1925.
6. Idem: Factors Modifying the Duration of Ventricular Systole, *J. Lab. & Clin. Med.* 6: 291, 1921.
7. Katz, L. N., and Feil, H. S.: Clinical Observations on the Dynamics of Ventricular Systole. I. Auricular Fibrillation, *Arch. Int. Med.* 32: 672, 1923.
8. Katz, L. N., and Siegel, M. L.: The Cardiodynamic Effects of Acute Experimental Mitral Stenosis, *AM. HEART J.* 6: 672, 1931.
9. Wiggers, C. J.: Studies on the Pathological Physiology of the Heart. II. The Dynamics of Aortic Insufficiency, *Arch. Int. Med.* 16: 132, 1915.
10. Feil, H., and Forward, D. D.: Clinical Observations on the Dynamics of Ventricular Systole. IV. Mitral Insufficiency and Mitral Stenosis. *AM. HEART J.* 8: 471, 1933.
11. Katz, L. N., and Feil, H. S.: Clinical Observations on the Dynamics of Ventricular Systole. III. Aortic Stenosis and Aortic Insufficiency, *Heart* 12: 171, 1925.
12. Feil, H. S., and Katz, L. N.: Clinical Observations on the Dynamics of Ventricular Systole. II. Hypertension, *Arch. Int. Med.* 33: 321, 1924.
13. Wiggers, C. J., and Maltby, Alice C.: Further Observations on Experimental Aortic Insufficiency. IV. Hemodynamic Factors Determining the Characteristic Changes in Aortic and Ventricular Pressure Pulses, *Am. J. Physiol.* 97: 689, 1931.

THE PRECORDIAL LEAD IN 104 NORMAL ADULTS*

ARTHUR H. MASTER, M.D.

NEW YORK, N. Y.

THE use of the precordial† ("chest" or "fourth") lead in the diagnosis of heart disease is rapidly increasing. Before clinical application of the precordial lead readings can be of value, it is necessary to have tracings of normal people as controls. Katz and Kissin¹ have published the measurements from records of 25 individuals, but a larger number is necessary before importance can be attached to the findings. These investigators placed their patients on the left side when taking the chest lead, but there is an objection to this procedure, as such a movement may shift and rotate the heart and hence change the electrocardiographic picture.

The 104 individuals whose records are reported in this paper were carefully examined at Cornell University Medical College in the years 1926, 27, 28. At that time the three standard leads of the electrocardiogram, and also anteroposterior and transverse chest leads were taken. Everything possible was done to make certain that the individuals were normal. They had no complaints; physical examination was negative; blood pressure tests, urine examinations, teleroentgenograms, electrocardiograms, exercise tolerance tests were all normal.

The series consisted of 26 women ranging in age from twenty-eight to sixty-five years, the average age being forty years, and 78 men from twenty-seven to seventy-four years old, the average age being forty-four years. In other words, it was a series comprised of normal adults.

The anterior electrode was placed near the lower end of the sternum, about the level of the apex of the heart and slightly to the left of the midline. The form of the electrocardiogram changed very little when this electrode was moved from the middle of the sternum to the region of the apex but not beyond. The posterior electrode was located on the back over the vertebral column at about the same level as the anterior or slightly higher. To the anterior electrode the wire from the right arm terminal of the galvanometer and to the posterior electrode the wire from the left arm terminal of the galvanometer were attached.

*From the Department of Medicine, Cornell University Medical College.

†The expression "precordial" lead is used in this paper synonymously with chest or fourth or anteroposterior lead.

TABLE I

	HEART RATE	SIZE		P-Q	SIZE		SIZE R	DURA- TION Q-R	SIZE T	DURA- TION T	TRANSI- TION R-T		DURATION R-T*
		P-WAVE	P-WAVE		Q	Q							
Average	77	-0.74 mm.	0.06 sec.	0.15 sec.	-5.3 mm.	+10.7 mm.	0.09 sec.	-3.3 mm.	0.19 sec.	-1.0 mm.			0.26 sec.
Range of 80% cases	60 to 85	-0.5 to -1.0	0.04 to 0.08	0.12 to 0.16	-3.0 to -7.0	+5.0 to +14.0	0.08 to 0.09	-1.5 to -4.0	0.16 to 0.24	-1.0			0.24 to 0.28
Low	50	-1.5	0.0	0.10	-1.5	+2.5	0.08	-1.0	0.08	0.0			0.20
High	100	0.0	0.10	0.18	-14.0	+17.5	0.10	-7.5	0.26	-2.0			0.32
Exceptional readings†	120	-2.0 +0.5 +2.0		0.20		+19.0 +23.0 +26.0	0.06						

*Measured from end of R through to end of T-wave.

†Each figure is obtained from the precordial lead of a single patient.

CHARACTERISTICS OF THE NORMAL PRECORDIAL LEAD

The P-wave was inverted; the amplitude averaged -0.7 mm. The average duration of the P-wave was 0.06 second. The limits are given in Table I where the measurements are summarized. At first glance, the P-wave (Fig. 1) appeared diphasic, for the interval between the P-wave and the QRS group was always slightly above the isoelectric level. This was due to the end deflection of the auricular contrac-

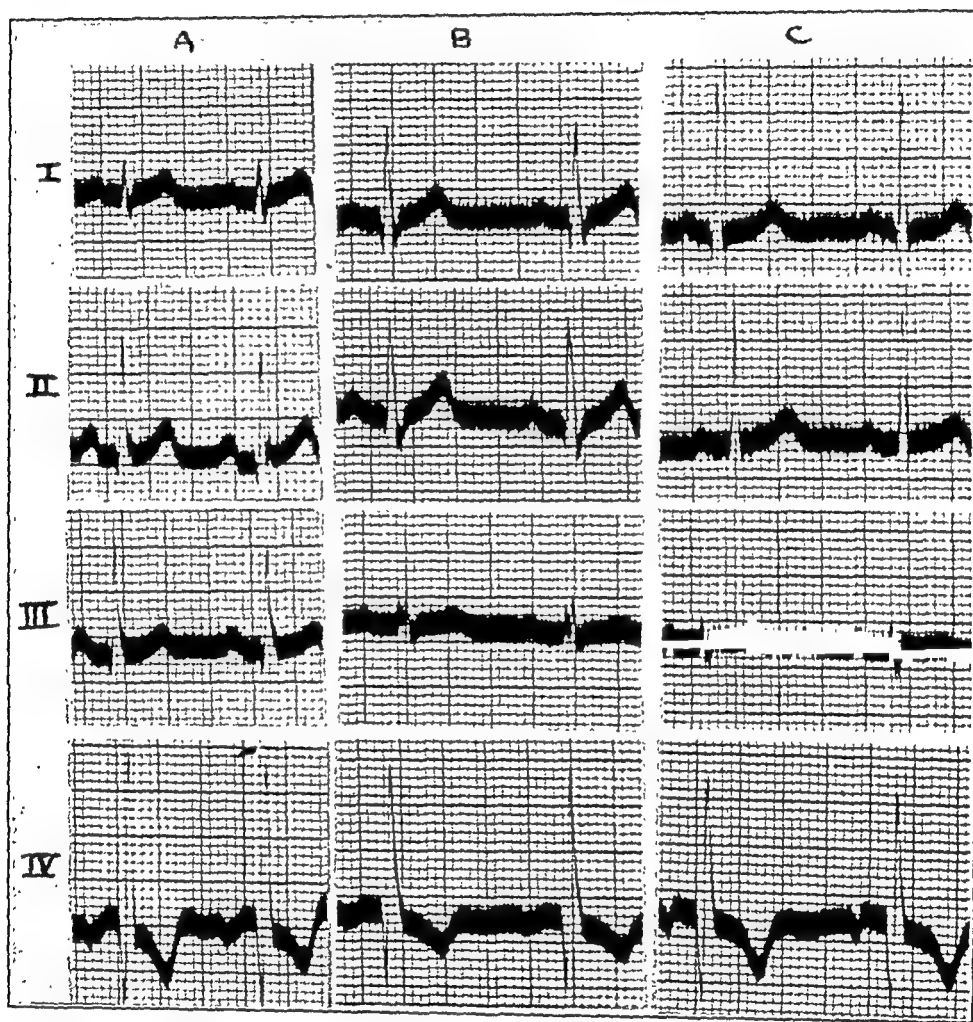


Fig. 1.—A, B, C, Three normal individuals with Leads I, II, III and precordial (chest or fourth) lead.

tion, the "T-wave of the P-wave," so to speak. In the standard electrocardiogram this end deflection of the P-wave is usually evident but is not so large as in the precordial lead.

The auriculoventricular conduction time, that is, the P-Q interval, measured 0.15 second, but the range was from 0.10 to 0.18 second. It attained 0.20 second once.

The QR group is perhaps a better term than the QRS group, for in the precordial lead there were only two waves visible. In the ordinary standard electrocardiogram three waves are common, and one

wave alone is not uncommon. In our series, the first wave of the QR group was always a downward deflection, or Q-wave. The absence of a Q-wave, therefore, is abnormal. The average size was -5.3 mm., but the amplitude ranged from -1.5 to -14.0 mm. Not one Q-wave measured less than -1.5 mm.

The next wave, the R-wave, was upright. Its average height was $+10.7$ mm., ranging usually from $+2.0$ to $+17.0$ mm., but attaining $+19.0$ mm., $+23.0$ mm., and $+26.0$ mm., each, once. The Q-wave was usually smaller than the R-wave, but to this there were eleven exceptions. The absence of an R-wave or one whose size is less than $+2.0$ mm. is abnormal.

The duration of the QRS was 0.09 second. In fact, the variation shown in this group was apparently much less than that in the standard electrocardiogram. It ranged, nevertheless, from 0.06 second to 0.12 second, each of these limits being attained only once, so that one is safe in stating that the upper limit of normal is 0.10 second. Notching or slurring was never present in the precordial chest lead of the normal individual. On the other hand, this is not uncommon in Lead III of the standard tracing.

The R-T transition of the precordial electrocardiogram differed from the RS-T transition of the standard record. The T-wave was angularly inverted almost immediately after the R-wave, with hardly a semblance of isoelectric level (Fig. 1). The average of the R-T transition was 0.08 second. The R-T interval, measured from the end of the downstroke of the R-wave to the end of the T-wave, was 0.26 second, but the range was from 0.20 to 0.32 second. The R-T transition usually was 1 mm. below the isoelectric level; it was isoelectric on eight occasions, but never once above the isoelectric line.

The T-wave was inverted. The negativity ranged in amplitude from -1.0 mm. to -6.0 mm. Once indeed it measured -7.5 mm. Any T-wave greater than -6.0 mm. is probably abnormal.

The average duration of the T-wave was 0.19 second, but there were wide variations, i.e., from 0.08 second to 0.26 second.

There were a few exceptions to the foregoing descriptions. The P-wave was positive in 2 instances out of the 104 examinations. This occurred in subjects of forty-eight and thirty years of age, respectively. These individuals were considered normal in every respect, but they had long, narrow hearts. It may be that an unusual rotation of the heart was responsible for these variations from the predominant findings.

The T-wave was barely positive once, about $+0.5$ mm. This was present in a woman forty-four years old in whom history, physical examination, teleroentgenogram of the heart and laboratory examinations were normal. Her electrocardiogram revealed a normal sinus rhythm with a left ventricular preponderance. The only doubtful

finding was an inverted cove plane T-wave in Lead III. The patient was reexamined in January, 1934. All examinations including fluoroscopy of the heart and lung were negative, but the precordial lead now revealed not only a positive T-wave of +0.5 mm., but a notched QR and an R preceding the Q-wave, an observation which is considered definitely abnormal and which was never found in any of the first 104 records. For these reasons it is my opinion that the inverted T-wave in Lead III was an abnormal finding, and that the patient did not possess a normal heart. Moreover, the fact that the slightly positive T-wave of the precordial lead was the only exception in the 104 cases proves that it may be discarded from a statistical point of view. In other words, a positive T-wave in the precordial lead should always be considered abnormal.

It appears from the foregoing that the precordial lead may help to decide when an inverted T-wave in the third lead of the electrocardiogram is of significance.

Left ventricular preponderance on the electrocardiogram occurred 44 times. The precordial tracings in these cases showed nothing different from those observed in the remaining cases.

COMMENT

Many types of electrodes were experimented with in taking chest leads. One of the simplest of these was an ordinary glass funnel, with outside diameter of about from 1.5 to 2 inches. Inside the funnel, as near the periphery as possible, were wound a few coils of thick copper wire which emerged through the narrow end. The funnel was stuffed with a wad of absorbent cotton moistened with warm salt water. The cotton was bulky so that it formed the area of contact with the chest wall. The glass, held in the hand, served as an insulator. Another such electrode was held in place posteriorly. I am now substituting the posterior chest electrode with the left leg electrode. As Wilson² has shown, the lead over the heart is the important one, and the other lead may be placed at a greater distance from the heart without significant changes in the electrocardiogram. I have confirmed this observation in at least 30 patients, and hence use the funnel electrode over the precordium, and the left leg as the indifferent electrode. The precordial lead is then taken as one ordinarily derives the standard Lead II. This method is simpler than utilizing both the anterior and posterior chest electrodes.

It was usually found unnecessary to rub the skin at the site upon which the funnel was placed, unless the chest was hairy. The best means of reducing resistance was by making two or three very superficial scratches with a hypodermic needle. It was never necessary to draw blood.

It will be observed that the P- and T-waves were inverted, and on this account many writers have suggested that the chest leads should be reversed. The P-wave would then be upright, the first wave of the QRS group would be upright, the second inverted, and the T-wave would be positive. In the standard electrocardiogram the waves usually occur in this form; hence the advantage of reversing the leads. The measurements given in Table I would still hold except that their signs would change.

SUMMARY

For the precordial lead the right arm electrode is placed on the anterior chest, just to the left of the sternum about the level of the apex, and the second electrode is on the left leg. The record is then taken as one usually derives Lead II of the standard electrocardiogram. This method is simpler than that of placing one electrode on the front and the other on the back of the chest.

A simple glass electrode is described for obtaining precordial leads.

It is suggested that the electrodes of the precordial lead be reversed so that P, R and T will be positive and only S inverted, just as they are in the standard electrocardiogram of normal adults.

The precordial chest lead in 104 normal individuals is summarized. In this series the P-wave is shown to be negative, is not more than -1.5 mm. and is usually followed by an end deflection above the isoelectric level. The P-Q interval averages 0.15 second. The QRS group is always diphasic, and never notched or slurred. Its duration is 0.09 second. The absence of the Q-wave or of the R-wave is definitely abnormal. The Q-wave averages -5.3 mm. in size and the R-wave, $+10.7$ mm. No Q-wave less than -1.5 mm. and no R-wave less than $+2.5$ mm. in size was ever observed. The R-T transition is below the isoelectric level, occasionally just isoelectric. A positive R-T transition or one that is more than 2 mm. below the isoelectric is definitely abnormal. The T-waves are always inverted and usually are less than -6.0 mm. in size.

The precordial lead may prove of service in interpreting which T-wave inversions of the third lead are abnormal.

Left ventricular preponderance in the standard electrocardiogram of normal adults does not change the form of the precordial lead.

My thanks are due to Dr. Harold E. B. Pardee for his many helpful suggestions.

REFERENCES

1. Katz, L. N., and Kissin, M.: A Study of Lead IV. Its Appearance Normally, in Myocardial Disease, and in Recent Coronary Artery Occlusion, *AM. HEART J.* 8: 595, 1933.
2. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1930.

THE EFFECT OF CONDENSERS IN THE ELECTROCARDIOGRAPH*†

MYRON SCHWARZSCHILD, M.A., AND MILTON KISSIN, M.D.
NEW YORK, N. Y.

THE taking of an electrocardiogram has certain commonly appreciated inconveniences. Compensation and current reversal are necessary; the string often tends to move off the field, and a well-trained operator is required. These difficulties are largely obviated by the use of a condenser (capacitance) in the electrocardiographic circuit, since the string then returns toward the center of the field automatically without the use of a compensating current. In fact, most of the amplifier type instruments available today make use of condensers.

A condenser placed in series with the patient and the electrocardiograph will suppress the low frequencies primarily due to "skin current" but will permit the passage of the cardiac current. A capacitance represents an impedance to the flow of electric current inversely proportional to the frequency of alternation of the current. It offers a practically infinite impedance to low frequency currents which are evidenced by a drift ("skin current"), whereas it offers little impedance to currents caused by the rapidly fluctuating heart voltage.

The use of the condenser has been mentioned before. Cremer¹ first reported its use for recording nerve currents. Later² he reported the possibility of its use in electrocardiography. Kraus and Nicolai³ mentioned the condenser as a means of automatic compensation, but on the basis of work done up to that time did not recommend its use because of the distortion introduced. Zwicke⁴ as well as Rothberger and Winterberg⁵ discussed the effect of the condenser qualitatively and showed that the magnitude of the distortion depends not only on the size of the condenser, but also on the value of the resistance of the circuit. Kahn⁶ and Weber⁷ noted the condenser as a method of compensation, and like Kraus and Nicolai³ did not advise its routine use because of distortion. Schellong⁸ presented tracings to illustrate the distortion introduced by condensers and showed that the effect of polarization is similar to that of capacitance. Lueg⁹ showed that the introduction of condensers (of small capacity—7 microfarads, 2 microfarads, and 0.5 microfarads capacity) into the string galvanometer circuit will cause flattening of the waves so that the records resemble those of myxedematous individuals.

*From the Physics Laboratory and the Department of Electrocardiography, Beth Israel Hospital, New York.

†Aided by a grant from the Herbert L. Celler Foundation.

Dock¹⁰ demonstrated the effect of condensers in the string galvanometer circuit, as well as the effect of capacitance in the amplifier type of electrocardiograph. He questioned the accuracy of records obtained with the amplifier type of instrument having condensers in the circuit. Ernstene and Levine¹¹ compared records taken with the amplifier type of electrocardiograph (circuit constants not given) with those taken with the string galvanometer. They found slight differences in the amplitude of the deflections of the two kinds of records, but considered amplifier records satisfactory. Pardee¹² expressed surprise at Dock's criticism¹⁰ (on the score of condensers) of the amplifier instrument. He made comparative records with both types of instruments and concluded that amplifier records do not show distortion and that high external ("skin") resistance will cause distortion in string galvanometer tracings, but not in amplifier records. Because of the predominantly qualitative trend of all the available data, a more thorough study from the quantitative point of view seemed desirable.

In the electrocardiograph there are two important sources of distortion. One is the distortion due to the imperfect mechanical properties of the recording system. The other is due to the imperfect electrical properties of the circuit. For electrocardiography, where very high frequencies (over 1,000 per second) need not be considered, these two types of distortion may be very simply differentiated in their effect on the record. The former, primarily due to the inertia of the moving system, is almost exclusively responsible for any loss of higher frequencies, because of the inability to follow very rapid fluctuations with fidelity.¹³ The latter, in all practical systems heretofore described, due to capacitance in the electrical circuit, is responsible for losses at low frequencies, resulting in a distortion, the details of which are the subject of this study.

METHOD

In order to investigate the distortion experimentally it appeared desirable to dispense with the use of patients as sources of voltage, since in an actual electrocardiogram slight variations in the waves occur from cycle to cycle. An artificial source which could be depended upon for exact duplication, with electrical properties similar to that of a patient, offers great advantages. Such a device was constructed. It consists essentially of a gas-filled photoelectric cell and a light source between which, with a suitable optical system, a disc is rotated by a spring motor. The disc is notched to correspond to the desired voltage waves. As it turns it occludes more or less light from the cell, thus causing more or less current to flow in the photo-cell circuit. A shunt in the circuit acts as the patient. The photo-cell current is high enough to permit the application of the voltage across

the shunt, the resistance of which may be made as low as 1,000 ohms, directly to the electrocardiograph without the interposition of amplifiers or other possible sources of distortion. With this device any recurring wave form may be produced at will by cutting the proper disc.

FACTORS DETERMINING THE MAGNITUDE OF THE DISTORTION

The simple circuit, consisting of galvanometer, condenser, and patient in series, is the basis for consideration. If at the beginning of a wave, say the R-wave, the condenser is uncharged, at the end of the wave it will be left with a charge. This charge on the condenser causes a deflection of the galvanometer opposite in direction to the wave

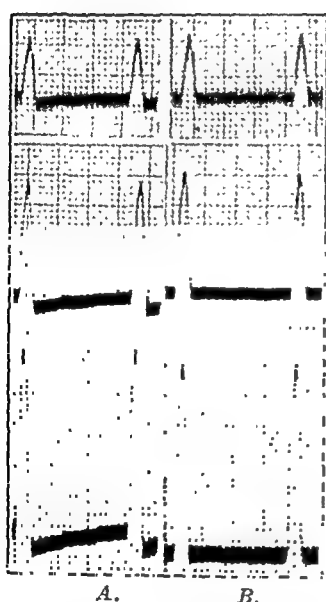


Fig. 1.

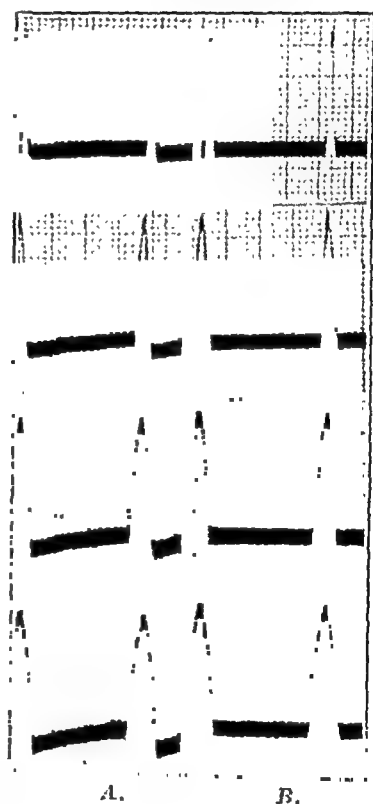


Fig. 2.

Fig. 1.—Effect of amplitude of the wave on the distortion: A, with condenser; B, without condenser.

Fig. 2.—Effect of duration of the wave on the distortion: A, with condenser; B, without condenser.

just terminated. The effect of the condenser is therefore to produce an overshooting of the end of the wave. In addition, during the course of the wave the condenser is accumulating the charge so that the amplitude of the wave will be reduced.

The actual extent of these distortions, that is the magnitude of the overshooting and the reduction in amplitude, depends upon the size of the wave being recorded and the constants of the circuit.

The distortion is proportional to the amplitude of the wave. This is illustrated in Fig. 1, which shows waves of 1, 2, and 3 millivolts, all having the same duration, produced artificially by means of the photo-

sensitive device. Fig. 1 *A* shows the waves as recorded with a condenser in the circuit, while Fig. 1 *B* shows the same waves as recorded without a condenser.

The distortion is also proportional to the duration of the wave. Fig. 2 shows waves of 0.05, 0.1, 0.15, and 0.2 second duration, all having the same amplitude. Fig. 2 *A* shows the waves as recorded with a condenser in the circuit, while Fig. 2 *B* shows the same waves as recorded without a condenser.

The distortion is inversely proportional to the product of the capacity of the condenser in farads and the resistance of the entire circuit in ohms. Since this product is known as the time constant, we may say that the distortion is inversely proportional to the time constant. This is illustrated in Fig. 3, which shows a series of waves all of the same amplitude and duration, as recorded without a condenser in the circuit, and with various time constants; namely, 3, 2, 1, 0.5, and 0.1 seconds. The time constant may be increased either by increasing the resistance of the circuit or increasing the capacity of the condenser.

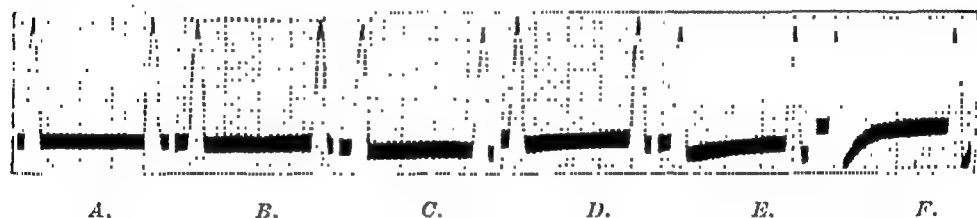


Fig. 3.—Effect of time constant on the distortion: *A*, without condenser; *B*, $\tau = 3$ sec.; *C*, $\tau = 2$ sec.; *D*, $\tau = 1$ sec.; *E*, $\tau = 0.5$ sec.; *F*, $\tau = 0.1$ sec.

The reduction in amplitude follows the same laws and is in general about half as great as the overshooting. Figs. 1, 2, and 3 verify this point.

CALCULATION OF THE DISTORTION*

In order to utilize these results to best advantage it is desirable to be able to calculate from a recorded wave the distortion contained in it; that is, for example, how much of a recorded depression of an RS-T interval is real and how much is due to the use of a condenser. In that way it will be possible either to correct records taken with inadequate condensers or to determine how much capacity is necessary for clinically satisfactory recording.

The quantitative relationships are very readily found. The charge delivered to the condenser during the passage of a wave is equal to the average current flowing in the circuit multiplied by the duration of the wave. The average current flowing in the circuit is equal to the average voltage divided by the resistance. If the wave is considered

*The mathematical details of the derivation of the formulas and statements embodied in this paper will be furnished, upon request, by the authors to those interested.

to be triangular in shape, a fair assumption, the average voltage is one-half the amplitude of the wave. Hence, if R is the resistance of the circuit, H is the amplitude of a wave and T its duration, the charge delivered to the condenser during its passage will be given by $\frac{HT}{2R}$. This charge, as has been stated before, causes a deflection of the galvanometer because a charge on a condenser is always accompanied by a voltage difference equal to the charge divided by the capacity of the condenser. In this case, then, the deflection of the galvanometer after the passage of the wave, or the overshooting, will be given by $\frac{HT}{2RC}$. The quantity RC in this expression is the time constant and will be denoted by τ so that finally the overshooting is given by $\frac{HT}{2\tau}$.

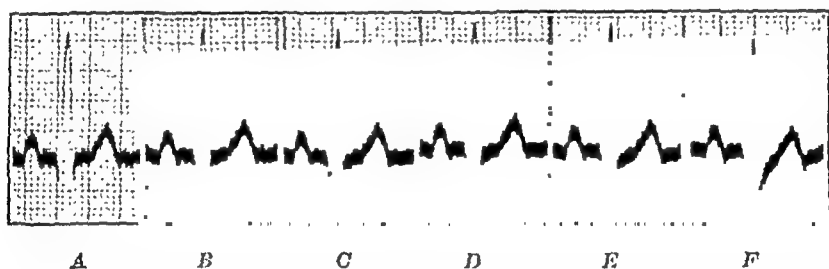


Fig. 4.—Artificial electrocardiograms with various time constants; agreement between calculated and measured values of the distortion: A, without condenser: RST depression 0.4 m.m., R amplitude 20; B, $\tau = 3$ sec. RST depression: Observed 0.5, Calculated 0.6, R amplitude: Observed 20, Calculated 19.9; C, $\tau = 2$ sec. RST depression: Observed 0.7, Calculated 0.7, R amplitude: Observed 20, Calculated 19.5; D, $\tau = 1$ sec. RST depression: Observed 1.1, Calculated 1.1, R amplitude: Observed 19.5, Calculated 19.6; E, $\tau = 0.5$ sec. RST depression: Observed 1.7, Calculated 1.9, R amplitude: Observed 19.5, Calculated 19.2; F, $\tau = 0.1$ sec. RST depression: Observed 6, Calculated 8.3, R amplitude: Observed 17, Calculated 16.

By a very similar argument it can be shown that the diminution of amplitude of the initial stroke of a wave is given by $\frac{Ht}{2\tau}$ where t is the duration of the initial stroke.

In order to simplify this discussion it has been assumed that at the beginning of the wave the condenser is uncharged. Actually, since any wave is merely one of a series of successive waves, this is not the case. If account is taken of the residual charge, the distortion calculated in accordance with the above formulas is, in an extreme case, in error by only 0.2 mm. for a time constant of one second and proportionately less for longer time constants. When all the waves are in the same direction, i.e., P, QRS and T, all erect or all inverted, the calculated distortion is slightly greater than the real distortion. When there are inverted waves, our formula may actually underestimate the distortions.

CLINICAL SIGNIFICANCE OF THE DISTORTION

Fig. 4 shows a series of artificial electrocardiographic curves taken with the help of the same photosensitive device mentioned above. It is readily seen that the most significant distortion from the clinical point of view is the depression of the RS-T segment due to the condensers. Inasmuch as attention is paid to the RS-T segment in the diagnosis of coronary artery disease, rheumatic fever, and other conditions, deviation of this segment assumes significance. Since the distortion is proportional to the size of the wave, small waves may show no distortion, while large waves will show appreciable distortion.

The time relationships, such as the PR interval, the width of the QRS straddle, the RR interval, remain unchanged with the use of condensers. This is readily verified in Fig. 4.

APPLICATION TO AMPLIFIER TYPE OF ELECTROCARDIOGRAPHS

This discussion applies directly only to the simple galvanometer circuit in which the patient, galvanometer, and condenser are in series.

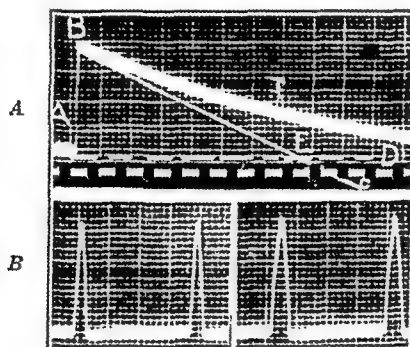


Fig. 5.—A, Determination of the effective time constant for an amplifier type electrocardiograph. B, Distortion introduced by this particular electrocardiograph.

The formulas may also be applied to amplifier type electrocardiographs in which condensers are used, if in place of τ , which for the simple circuit is the product of the capacity of the condenser in farads and the total resistance (galvanometer and patient) in ohms, is substituted the equivalent time constant.

The equivalent time constant may be determined by applying a potential of a few millivolts to the leads without a patient. The record obtained will show a sudden rise and then a gradual drop back to the isoelectric line. Fig. 5 A shows such a record. If the straight line BC is drawn tangent to the curve at the peak, the time between the initial rise and the intersection E, with the zero line, AD, measured in seconds, is the equivalent time constant, in this case 1.4 seconds.

Fig. 5 B shows the distortion introduced by the instrument, the time constant of which is derived in Fig. 5 A.

In the string galvanometer with condensers in the circuit, changes in the patient's resistance will affect the time constant, whereas in the amplifier instrument as generally constructed the time constant is independent of the patient's resistance.

OPTIMUM TIME CONSTANT

One of the advantages of the condenser, cited above, is the saving of time in shifting from lead to lead. If the time constant is long, this advantage disappears, since it may require the lapse of a considerable period of time for the string to reach its normal position after a shift of leads. The time required is proportional to the time constant and to the difference in the constant voltage (skin current) between the two leads. Too long a time constant, therefore, entails a loss of the advantages of the condenser.

It is desirable to arrive at a minimum time constant which will not cause distortion of clinical significance. With the help of the

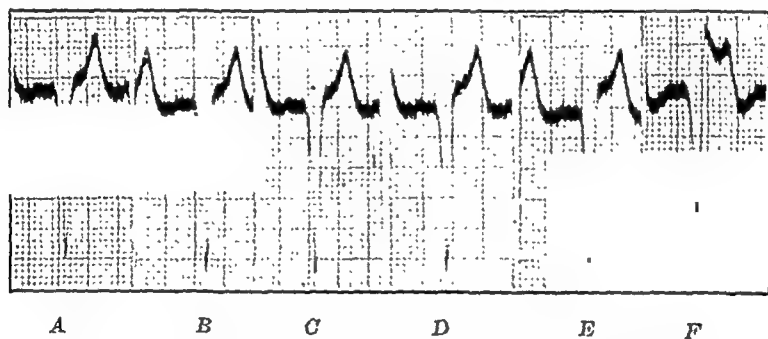


Fig. 6.—An extreme case in which there is measurable distortion even for a time constant of 2 seconds: A, no condenser; B, $\tau = 3$ sec.; C, $\tau = 2$ sec.; D, $\tau = 1$ sec.; E, $\tau = 0.5$; F, $\tau = 0.1$ sec.

formula for determining the depression at the end of a wave, we may reason as follows. The most important clinical distortion is the depression of the RS-T segment. With an R-wave of 0.1 second or less in duration, and 20 mm. or less in height, a time constant of 2.0 seconds would introduce a depression of the RS-T segment of 0.5 mm. or less. Therefore, 2.0 seconds is perhaps the optimum value for the time constant.

Even with a 2.0 second time constant there may, in exceptional cases, still remain some distortion of possible clinical significance. Fig. 6 shows a series of electrocardiograms taken on an actual patient with and without condensers. Various time constants were used as indicated.

With a 2.0 second time constant there is an increase in the elevation of the T take-off by 0.6 mm., which may still be significant. Hence in such an exceptional case (high and wide wave) an even longer time constant is necessary for distortionless recording, or the calcu-

lated value for the overshooting should be deducted from the observed deviation to arrive at the real value.

USE OF THE CONDENSER WITH STRING GALVANOMETER

In case ease of shifting leads is of importance, the condenser in the string galvanometer must be connected at a point in the circuit beyond the lead changing switch. The string protecting switch (short-circuiting type) should be connected so that it will not short circuit the condenser through the string. With these connections properly made, switching from lead to lead involves only three motions. First, the string protection is put on; second, the lead is changed; and third, the string protection is removed. With a skin voltage difference between two leads of 15 millivolts and with 500 mf. (3.5 second time constant) the string protection must be left on for six seconds in order that the string may be practically at the center of the field when the protection is removed. For other conditions the time may easily be computed, as it is proportional to the time constant and the difference in skin voltage.

Paper condensers of large capacity are expensive, heavy, and bulky. It is possible to use electrolytic condensers which reduce the expense, the size and weight considerably. They must be connected in such a way that the normal polarizing voltages found in such condensers may be neutralized. This can be done by connecting them in a bridge arrangement. By this means a satisfactory condenser of 500 mf. may be constructed which will weigh about 5 pounds and occupy a space of only 8" \times 7" \times 6".

When using the condenser, it is desirable to use short-circuiting string protection such as is used in most of the more recent string electrocardiographs.

The most important uses for the condenser are as follows:

1. For taking one lead over a long period of time without watching the string. Adventitious movements will not throw the string off the field. The tracing will go along evenly, it will look better, and will be easier to read.

2. For use when only an untrained assistant is available. A trained person can set up the machine and an untrained individual may then operate it.

3. For taking tracings of the three leads where rapid shifting from lead to lead is necessary, and time relationships rather than the fine details of the form of the electrocardiogram are being studied. In this case a condenser of relatively low capacity should be used. Such records may be corrected by the use of the formulas given above.

SUMMARY

1. Condensers placed in the string galvanometer or amplifier type of electrocardiograph make compensation for "skin current" auto-

matic. String galvanometers are not ordinarily equipped with condensers; whereas most amplifier electrocardiographs are so equipped.

2. The presence of condensers introduces distortion.

3. The chief distortions that may be introduced by condensers in the electrocardiograph in clinical practice are RS-T deviation and diminution in the height of the R-wave. Since attention is paid to the RS-T segment in the diagnosis of coronary artery disease, rheumatic fever, etc., its deviation is significant. The time relationships are unaltered.

4. The magnitude of the distortion is proportional to the duration and amplitude of the wave being recorded and is also, in a simple circuit (string galvanometer), inversely proportional to the product of the resistance and capacity.

5. This product is known as the time constant. An amplifier circuit (which is a series of simple circuits) has an equivalent time constant to which the distortion is likewise inversely proportional. A simple method is given for determining this constant.

6. Formulas are given for determining the magnitude of the distortion.

7. If the time constant of the circuit is 2.0 seconds or more, the distortion is not usually significant in clinical practice.

REFERENCES

1. Cremer, M.: Ueber die galvanometrische Beobachtung und Registrierung der Aktionsstroeme im offenen Kreise, Sitzungsber. der Gesellsch. f. Morphol. u. Physiol. in München 21: 7, 1905.
2. Idem: Verh. d. Kong. f. innere Med. 23: 724, 1906.
3. Kraus, F., and Nicolai, G. F.: Das Elektrokardiogramm des gesunden und kranken Menschen, Leipzig, p. 72, 1910, Veit & Co.
4. Zwick: Die Verwendung des Kondensators bei der Aufnahme des Elektrokardiogramms, Ztschr. f. Biol. 56: 32, 1911.
5. Rothberger, C. J., and Winterberg, H.: Ueber Extrasystolen mit Kompensatorischer Pause bei Kammerautomatie u. ueber die Hemmungswirkung der Extrasystolen, Pflüger's Arch. f. d. ges. Physiol. 146: 390, 1912.
6. Kahn, R. H.: Das Elektrokardiogramm, Ergebn. d. Physiol. 14: 18, 1914.
7. Weber, A.: Die Elektrokardiographie und andere graphische Methoden in der Kreislaufdiagnostik, Berlin, p. 22, 1926, Julius Springer.
8. Schellong, F.: Ueber exakte und nicht exakte Registrierung des menschlichen Elektrokardiogramms, Klin. Wchnschr. 5: 541, 1926.
9. Lueg, W.: Die Polarisationskapazität der Haut und der Gewebe als Fehlerquelle bei der Auswertung klinischer Elektrokardiogramm, Klin. Wchnschr. 9: 606, 1930.
10. Dock, W.: Distortion of Electrocardiogram by Capacitance; Critical Analysis of Electrical Amplification of Heart Currents, AM. HEART J. 4: 109, 1928.
11. Ernstene, A. C., and Levine, S. A.: A Comparison of Records Taken With the Einthoven String Galvanometer and the Amplifier-Type Electrocardiograph, AM. HEART J. 4: 725, 1929.
12. Pardee, H. E. B.: The Distortion of the Electrocardiogram by Capacitance, AM. HEART J. 5: 191, 1929.
13. Caldwell, S. H., Oler, C. B., and Peters, J. C.: An Improved Form of Electrocardiograph, Rev. Scient. Instruments 3: 277, 1932.

A SELF-RETAINING SKIN CONTACT ELECTRODE FOR CHEST LEADS IN ELECTROCARDIOGRAPHY*

IRVING R. ROTH, M.D.
NEW YORK, N. Y.

SINCE the introduction of the electrocardiographic Lead IV by Wolferth and Wood in January, 1932, the study of chest leads has taken on considerable impetus. Many workers are now investigating the subject with the hope of finding some lead or leads that will disclose evidences of myocardial damage not revealed by the standard three leads originally adopted by Einthoven for clinical electrocardiography. In

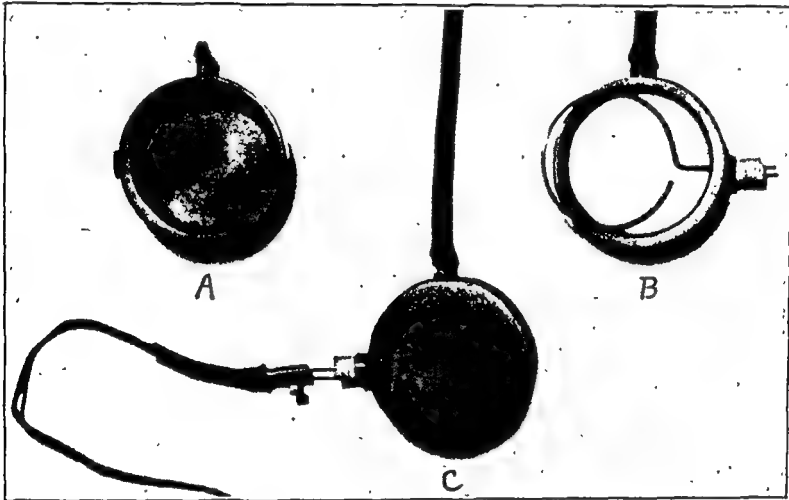


Fig. 1.—A, hard rubber cup (described in text). B, Electrode partly assembled; bottom of cup contains moist wool pad and copper loop is partly in place. C, Completely assembled electrode.

the successful pursuit of the study of chest leads, one requires a suitable electrode which will satisfy the following requirements:

1. That the electrode cover a *small surface*, to enable the investigator to "tap" the "potential" over selected small areas. This is essential because the potentials over the chest wall vary appreciably from point to point, even when these are one or two inches apart.

2. That the electrode be *completely insulated*. This is to prevent contact with adjacent areas of skin or other sources of extraneous potentials.

3. That the electrode *retain its position* absolutely. A sliding electrode may produce artifacts.

4. That the electrode offer a *low resistance* to the circuit. Overshoot of the galvanometer string is to be avoided if we are to evaluate

*From cardiographic laboratories of the Mount Sinai Hospital, New York City.

tracings of chest leads, particularly during this initial stage of our investigation of chest leads.

With these requirements in mind I have constructed an electrode, illustrated in Fig. 1. It consists of a hard rubber cup, about a half inch deep and about one and three-quarter inches in diameter.* Within the cup there is a copper loop between two pads of wool. The free end of the copper loop protrudes through an opening in the side of the cup. A small perforated rubber stopper slides over the end of the wire. This stopper fits the opening in the side of the cup and serves to seal the exit of the wire. Into another opening in the side of the cup there is fitted a small nozzle to which a rubber tube is attached for the purpose of producing a partial vacuum within the cup, when in use. An elastic band is stretched over the free margin of the cup with sufficient overlapping to keep the contents in place.

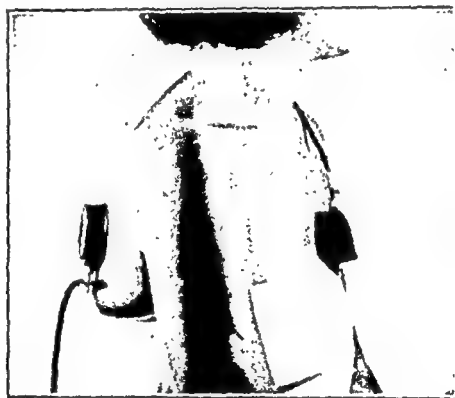


Fig. 2.—Electrodes in situ, retaining their position on chest wall.

METHOD OF ASSEMBLING ELECTRODE AND APPLYING IT TO THE CHEST WALL

1. Place one *moist* wool pad into cup.
2. Introduce copper loop, with free end protruding through opening in the side of the cup.
3. Holding loop in place with thumb, slip perforated rubber stopper over free end of wire, and by gentle rotation, force stopper into opening of cup and press it firmly into place. To test whether stopper has sealed opening, invert cup over palm of hand, press firmly and make slight suction on nozzle. If stopper is firmly in place, such suction must produce a partial vacuum sufficient to hold cup against palm.
4. Place a second *moist* wool pad into cup.
5. Stretch elastic band over free margin of cup with sufficient overlapping to hold contents in place (elastic band should overlap about one-eighth inch).

*The set consists of three electrodes. Two of these have dimensions as specified above. The third is smaller—surface diameter only one and one-quarter inches. This is useful in case one wishes a more accurate localization in the region of the apex impulse of the heart.

With proper preparation of skin, these smaller electrodes may be used exclusively.

6. Put assembled electrode into warm (not hot) salt solution, from three to five minutes.

7. Select area on chest wall where electrodes are to be applied.

8. Cleanse area with water and alcohol and rub vigorously with moist coarse cloth until skin is flushed (if skin is too thick and cannot produce flush, one may make a small superficial scratch with a dull, sterile needle point).

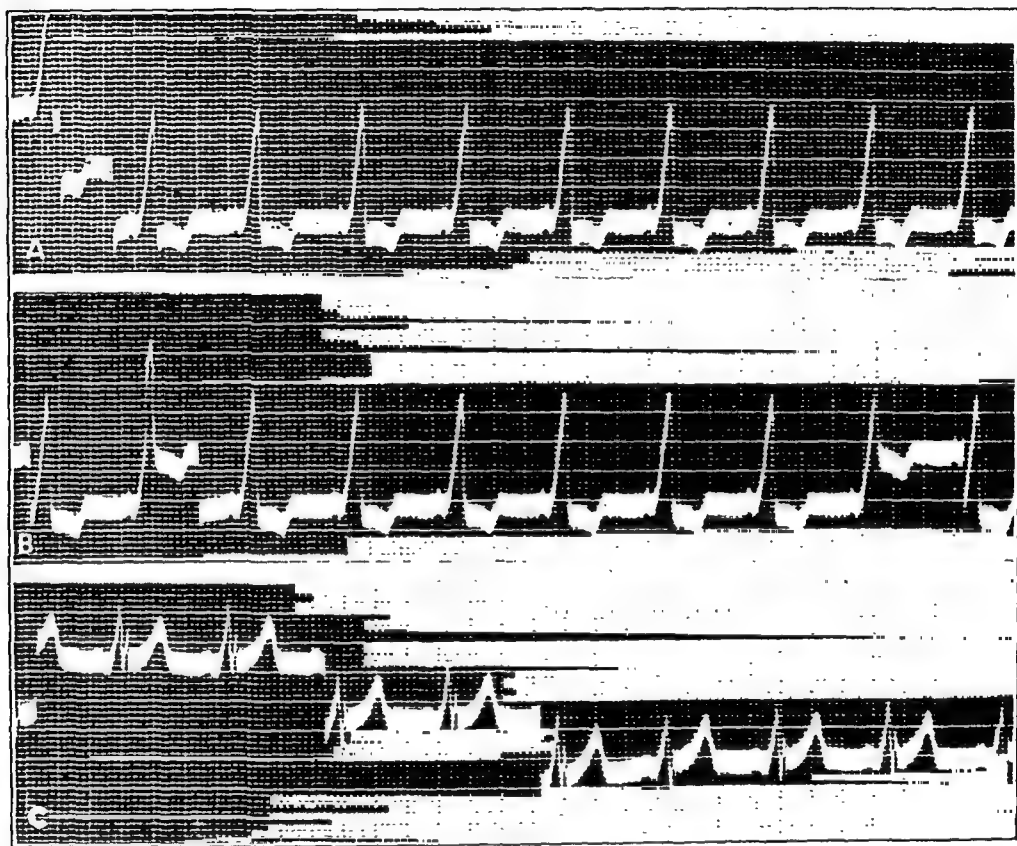


Fig. 3.—A, Conventional Lead I taken in usual manner, large surface contact, salt water bandages containing a large German silver plate. B, Conventional Lead I taken with electrodes here described, held in place over the anterior surfaces of right and left forearms. C, Chest lead taken with self-retaining electrodes of one and three-quarter inches surface area. The right electrode was applied one inch above and mesad to angle of right scapula. The left electrode was applied three inches lateral to left sternal margin in fourth interspace.

9. Remove electrodes from salt solution; express excessive water; wipe cup dry, especially protruding wire; make contact between end of copper wire and "lead" cable; attach soft rubber tube to nozzle.

10. Place cup over selected area; press firmly against chest wall. While pressing, produce partial vacuum through rubber tube (use medium-sized syringe and produce vacuum sufficient to collapse rubber tube). Clamp tube. Proceed to take the electrocardiogram (see Fig. 2).

CAUTIONS TO BE OBSERVED

1. Do not permit cable to drag on the electrodes.
2. Patient should be relaxed and cautioned not to move about, lest he stretch his skin and dislodge electrodes.
3. In case of male patients, the area selected may have to be shaved.
4. Copper loops must be clean. Scrape before using, or replace by new one frequently.
5. After electrocardiogram has been recorded, electrodes should be taken apart, being careful not to bend copper loop when removing rubber stopper. Parts should be washed and dried so as not to permit the accumulation of salt crystals.
6. *Never boil* hard rubber cup. Hot water will distort it.

The instrument is essentially a vacuum cup containing the electrode. As such, after it has been applied for some time it may leave a hyperemic zone which, for cosmetic reasons, may be undesirable on the part of some patients. In such a case the electrode may be used without suction. It can be applied to the chest wall in the same manner as one would apply a stethoscope bell. If the skin is prepared, satisfactory tracings can be taken in this way. An assistant or the patient himself may hold the electrodes in place.

The resistance with these electrodes may safely range from 1 to 4000 ohms without overshooting of the galvanometer string. Higher resistances have been found satisfactory, but as a general rule they should be avoided.

Tracings taken with these electrodes are shown in Fig. 3. Fig. 3A shows tracings taken in the usual manner—large plates and salt water bandages. Resistance, 1500 ohms. Fig. 3B shows tracing taken from extremities with self-retaining small electrodes. Resistance, 2500 ohms. Fig. 3C shows chest lead from same patient. Resistance, 750 ohms.

SUMMARY

A new skin contact electrode for electrocardiographic work is presented. This electrode is of small surface, completely insulated, of low resistance and is self-retaining. It is hoped that it will facilitate in particular the study of chest leads in electrocardiography.

AN EFFICIENT APPARATUS FOR SIMULTANEOUS ELECTROCARDIOGRAPHIC AND ARTERIAL PULSE RECORDS*

J. EDWIN WOOD, JR., M.D., AND R. J. GENTILE, B.S.
UNIVERSITY, VA.

ARTERIAL pulse curves are not infrequently of value, especially in medical teaching. Combined electrocardiographic and arterial pulse records often serve to elucidate the various cardiac arrhythmias. Difficulties attendant upon the proper recording of simultaneous arterial and electrocardiographic curves are based partly upon inefficiency of

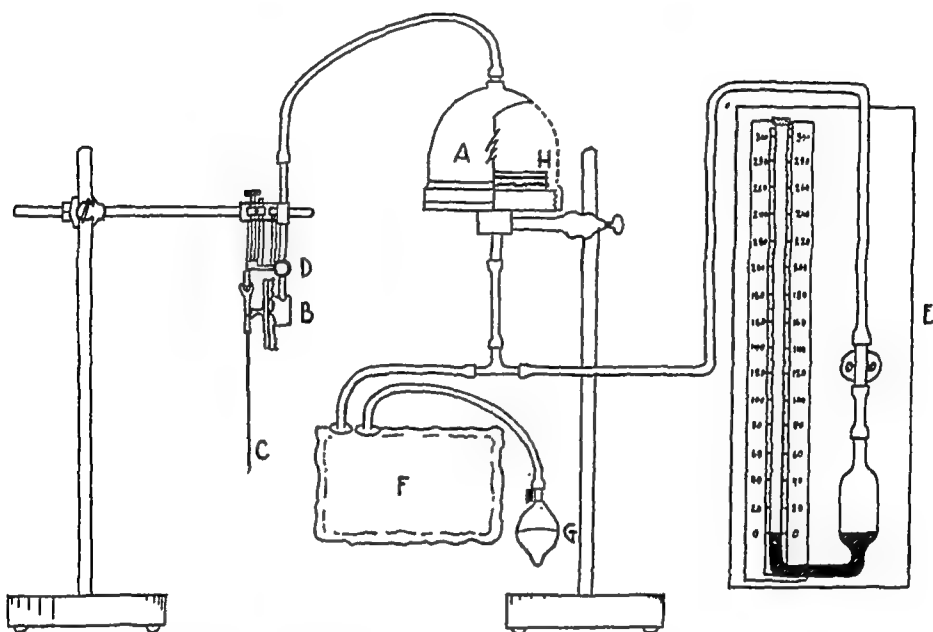


Fig. 1.—A, Erlanger metal bell. B, recording tambour with recording lever C and escape valve D. E, mercury manometer. F, clinical blood pressure cuff with usual bulb and valve G.

the average receiving tambour or glycerin pellote and occasionally upon the observer's lack of familiarity with their use. The apparatus described below obviates both of these difficulties as it requires no particular adjustment and invariably permits a good excursion of the arterial recording lever. Application of a clinical blood pressure cuff is the only adjustment necessary for reception of the arterial impulse when used with an Erlanger bell, and a recording tambour. The cuff may be pumped up and left in place so that one person may operate both galvanometer and arterial lever and easily obtain a double record (Fig. 2a). While a combination of the Erlanger capsule with arterial pulse levers has been previously suggested,¹ it is thought that the particular arrangement indicated below will be useful and therefore worthy of description.

*From the Department of Internal Medicine, School of Medicine, University of Virginia, University, Va.

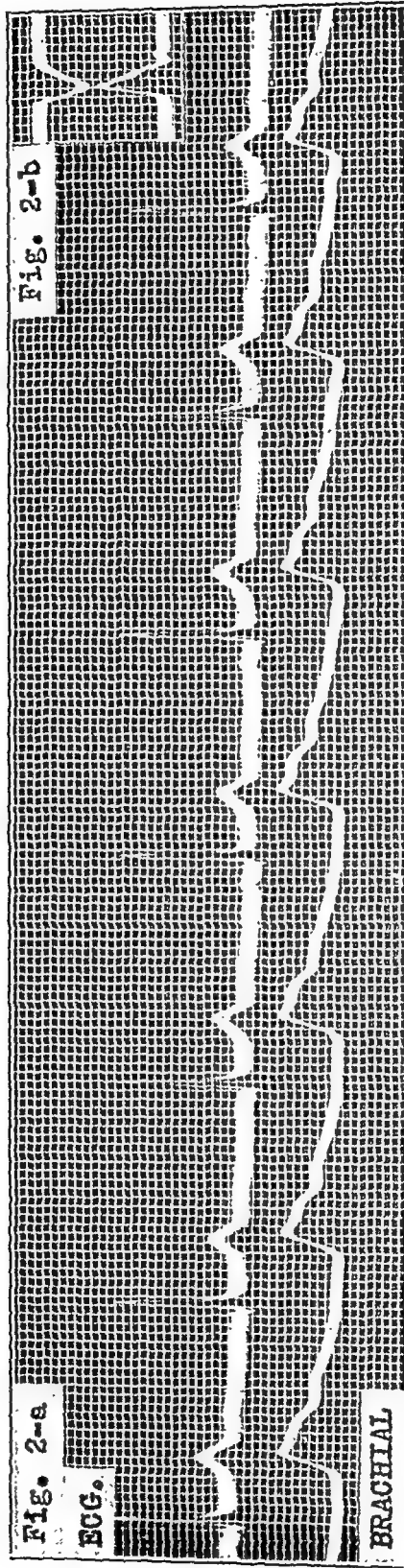


Fig. 2.—(a) Simultaneous electrocardiogram, Lead II, and brachial pulse curve from right arm. The arterial curve is displaced to the right by approximately 0.026 second. (b) Record of delay from cuff *P* to recording lever *C*. For method of calculation see text.

APPARATUS AND METHOD

The accompanying diagram (Fig. 1) is practically self-explanatory. An Erlanger metal bell (A), the base (H) of which has been covered

with three layers of rubber dam, is placed between an ordinary clinical blood pressure cuff (F) and simple recording tambour (B). Clinical mercury manometer (E) is attached on the cuff side of the system by a T-tube. Light broom straw recording lever (C) is placed vertically in front of the camera aperture of the electrocardiograph. Electrodes are attached as usual, the blood pressure cuff is applied to the arm, pumped to the approximate diastolic pressure of the patient, and the tracing taken. The resulting curves are smoother and of a more usual contour if a slight air escape is allowed in the recording tambour at valve (D).

The best excursions of the arterial recording tambour have been obtained when three layers of rubber dam (weight, approximately 1.1 oz. per sq. ft.) have been used at H. A single layer of much lighter rubber membrane should be used on tambour (B).

ERROR AND CORRECTION

Delay in the air system between cuff (F) and recording lever (C) has been calculated by a simple and direct method. Cuff (F) is rolled up tightly, a light broom straw placed between its folds with four or five cm. of broom straw projecting beyond the edge of the cuff. The rolled cuff is then placed in a claw clamp and adjusted so that the shadow of the projecting broom straw will fall on the camera aperture parallel to recording lever (C). If the cuff is then pumped up to 80 mm. Hg and compressed sharply with thumb and forefinger, there is an immediate movement of the straw held tightly in its partially distended folds and a corresponding response of lever (C). Movement of the broom straw in cuff and the resultant movement of lever (C) may be photographed with the electrocardiographic camera, and the delay from cuff (F) to lever (C) indicated. For example, from the beginning of the upper curve of Fig. 2b to the beginning of the lower curve there is a delay of approximately 0.026 sec., as measured with a Cambridge Record Measurer. The brachial curve shown in Fig. 2a is therefore displaced to the right by this interval. Thus the apparatus does not exceed in error instruments previously used; Lewis² has stated the delay in transmission through the air of the rubber tubing to be approximately 0.03 sec. in the radial and brachial curves shown in his book. Ordinarily the patient may be placed close to the galvanometer so that the distance from the cuff to recording tambour is not more than two or three feet. However, satisfactory tracings may be obtained with the patient as far away as nine or ten feet from the instrument, with a slight additional delay in the arterial record.

REFERENCES

1. Halsey, R. H.: *Arch. Int. Med.* 17: 540, 1916.
2. Lewis, Sir Thomas: *The Mechanism and Graphic Registration of the Heart Beat*, London, ed. 3, 1925, Shaw & Sons, Ltd.

Department of Clinical Reports

COARCTATION OF THE AORTA*

REPORT OF A CASE IN WHICH SUDDEN DEATH WAS DUE TO RUPTURE OF THE AORTA

HAROLD L. STEWART, M.D., AND S. BELLET, M.D.
PHILADELPHIA, PA.

THE embryology, pathological anatomy, clinical features, and pathological physiology of coarctation of the aorta as well as the roentgenographic findings in cases have been reported on in detail, not only in Abbott's classical contribution to this subject, but also in the papers of King,¹² Woltman and Shelden,¹⁸ Rösler,¹⁵ Blackford,¹ Railsback and Dock,¹⁴ Thomson and Lamb,¹⁶ Fray,⁸ Ernstene and Robins,⁵ Blumgart, Lawrence and Ernstene,² Lemon,¹³ East,³ Hampson,¹⁰ Ulrich,⁷ Evans,⁶ and Eppinger and Midelfart.⁴ The object of the present communication is to report a case in which death was due to rupture of the aorta following a dissecting aneurysm. In addition some studies of the arteries above and below the point of coarctation were made to determine the effect of the wide variation in pressure upon these vessels.

J. W., a white male, aged twenty-six years, an Italian laborer, was admitted to Jefferson Hospital in a state of shock. He had always been healthy and recalled no illnesses, aside from slight colds. The family history contained nothing of note. On November 14, 1930, the patient went to work feeling quite well. While carrying a heavy timber he was seized with pain in the "pit of the stomach." This was so severe that he was compelled to drop his burden. He nevertheless continued to work for several hours, although still experiencing severe pain in the upper abdomen. He remained in bed for two days, following which the pain gradually subsided. On November 17 he returned to work, feeling better, although his discomfort had not entirely disappeared. Upon lifting a heavy block of wood he was again seized with a pain which was so much more severe and agonizing than that previously experienced that he collapsed. He was brought to the hospital in a state of shock but was able to answer questions.

The pain was localized in the lower left chest and upper abdomen and was aggravated by deep inspiration. Examination revealed a well-developed adult male with shallow respirations. There were visible pulsations of the vessels of the neck. The chest appeared distended over the lower left anterior portion. The heart was slightly enlarged in the transverse diameter; the sounds were of good quality, and a systolic murmur was audible at the apex. The pulse was regular, the rate ranging from 90 to 112. The blood pressure in the right arm ranged from 126/60 to

*From the Laboratories of Pathology of the Jefferson Medical College and Hospital and the Philadelphia General Hospital aided by the Martin Research Fund.

136/60. The blood pressure of the legs was not recorded. A slight bulge was observed in the upper left quadrant of the abdomen, and the rectus muscle in this region was extremely tender and rigid. No masses were palpable.

The day following admission he appeared fairly comfortable under morphine. His temperature, which was normal on admission, rapidly rose to 102°. His pulse ranged from 90 to 112 and respirations from 20 to 24 per minute. Blood count and blood chemistry were normal. The urine showed a trace of albumin and hyaline casts. Blood Wassermann reaction was negative, and the icterus index was 9.2. The patient was in the hospital but two days, and his condition was so grave that complete studies were not made. Death occurred suddenly at 1 A.M. on November 19. The diagnostic impression was that of an acute cardiac or intraabdominal calamity, the exact nature of which was not determined.

Post-mortem Examination.—The chief findings of interest were confined to the heart, aorta and its branches. The pericardial sac contained 700 c.c. of partially



Fig. 1.—Heart showing upper portion of ventricular septum (left) with aorta attached; (1) subaortic stenosis; (2) irregularly widened aortic cusp; (3) aortic tear just above cusps; (4) dissection aneurysm; (5) point of coarctation.

clotted blood. The heart was definitely enlarged, its weight being 870 gm. Both ventricles were dilated and hypertrophied, this being more marked in the left ventricle. The musculature, however, appeared normal in color and consistency. The left ventricular wall at its midportion measured 25 mm., the right 8 mm., the mitral valve measured 8 cm., pulmonic 7.5 cm., the tricuspid 12 cm. and the aortic 8.1 cm. The cusps of the aortic valve varied somewhat in width; the right anterior measured 3.1 cm. and the left 2.6 cm.; the posterior 2.4 cm. at the free margin. A moderate subaortic stenosis was present. The ascending aorta was dilated and tended to form a distinct aneurysmal sac. The aorta 3 cm. from its origin measured 8.4 cm.; 6 cm. from its origin 7.5 cm. Immediately above the right anterior leaflet was a complete semicircular tear in the aorta measuring 2.5 cm. in its longest diameter (Fig. 1). A fresh thrombus protruded through the point of rupture and extended into the pericardial sac. Beginning at the origin of the aorta was a dissecting aneurysm which extended upward between the media and adventitia

of the ascending and transverse portion and separated the corresponding coats of its main branches. Twelve cm. from the origin of the aorta and immediately below the insertion of the ductus arteriosus was an almost complete obliteration of its lumen. The marked stenosis was the result of narrowing at that point and in addition of the interposition of a smooth fibrous diaphragm which was concave toward the heart and convex toward the thoracic aorta, ending in a small papilla which admitted only the passage of a bristle. The openings of the innominate, left common carotid and left subclavian arteries were considerably dilated and the vessels thickened and tortuous. The internal mammary and the other arteries arising from the subclavian trunk, particularly on the right, were also dilated, thickened and tortuous. The lumen of the aorta was small and its wall much thinner below the point of coarctation. The openings of the first aortic intercostals were small, but those of the second, third, fourth, fifth, sixth and the bronchial, together with the other branches of the abdominal aorta, were markedly dilated. There was no evidence of atherosclerosis or syphilis.

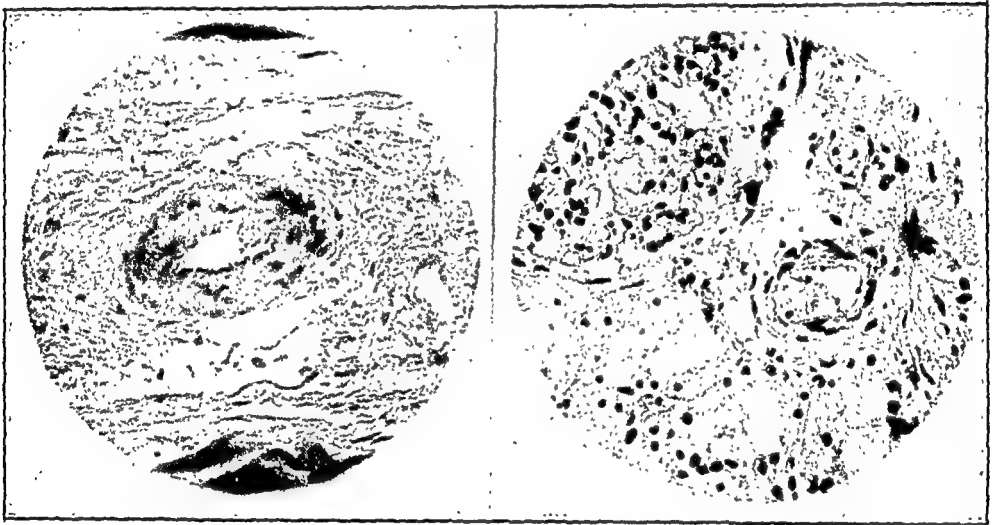


Fig. 2.

Fig. 3.

Fig. 2.—Small arteriole in myocardium. Note relation between thickness of vessel wall and diameter of lumen. Compare with Fig. 3.

Fig. 3.—Two small arterial branches in the kidney. Note relation between thickness of vessel wall and diameter of lumen. Compare with Fig. 2.

Microscopic Examination.—Thin pieces of the various tissues were fixed in 10 per cent formalin and Zenker's fluid. They were cut and stained with hematoxylin and eosin, Mallory's and van Gieson's connective tissue stains, Verhoeff's stain for elastic tissue and phosphotungstic acid stain for fibroglia. The heart muscle showed evidence of hypertrophy of its fibers and slight granular degeneration. The chief finding of interest was the marked thickening of the walls of the smaller sized arteries. (Fig. 2.) This hypertrophy involved musculature as well as internal elastic lamina. The larger branches of the pulmonary artery were unchanged. The smaller ones showed hyperplasia, reduplication and fraying of the internal elastic lamina. The branches of the bronchial arteries were unchanged. The smaller arteries and arterioles in the organs supplied by the aorta below the point of coarctation were normal (Fig. 3).

Sections of the aorta just above the cusps and proximal to the tear showed marked thickening of the vasa vasorum. Red cells, many large polyblasts and a few fibroblasts were seen lying between the layers of the media and adventitia and between the frayed muscle fibers of the media which contained quite a considerable

amount of basophilic ground substance in which the collagenous fibers were embedded and which was areolar in arrangement. The elastica of the inner portion of the media was fairly well intact, although that in the outer portion of the media was considerably frayed and broken up. Sections from the torn flap of the aorta showed in addition to the changes just described an enormous amount of fluid and blood especially in the media and also between the intima and the media, necrosis of the media, extensive interruption of all the elastic tissue and an increase in collagen in the inner fifth of the media. Sections from the descending thoracic aorta below the point of coarctation showed that part of the vessel to be thin due to medial hypoplasia; the inner portion of the intima had a vacuolated appearance and showed considerable metachromatic connective tissue which stained red with van Gieson's stain.

The pathological diagnosis was coarctation of the aorta of the adult type; cardiac enlargement due chiefly to hypertrophy; subaortic stenosis; unequal width of aortic cusps; aneurysmal dilatation of ascending aorta; dissecting aneurysm with rupture; hemopericardium; hypoplasia of the aorta distal to point of coarctation; passive congestion of the liver, spleen and kidneys; hypertrophy of the media and of the internal elastic lamina of the branches of the coronary arteries and arterioles; hyperplastic sclerosis of the small branches of the pulmonary artery.

COMMENT

The presence of the thickened arterioles observed in the heart is worthy of discussion. Although the systolic blood pressure reported in this case was 136 mm., this was obtained while the patient was in a state of shock; and from our knowledge of these cases, together with the cardiac enlargement observed, it seems reasonable to suppose that his blood pressure before the accident was considerably higher. Hypertension above the point of coarctation had probably been present for many years. In long standing, essential hypertension the associated sclerotic lesions of the smaller branches of the renal arteries and of similar vessels elsewhere, is believed by many to be the result of hypertension, although this point has not definitely been settled. In the case of coarctation, it is interesting to study this point because the patients have a high blood pressure proximal to the coarctation and a low blood pressure distally. It is interesting to observe the effect of hypertension in one part of the body and a normal or lower tension in the remaining portion in the same individual. Hypertrophy of the media and internal elastica in the smaller arteries is considered to be a stage of arteriosclerosis (Fishberg;⁷ Kernohan, Anderson and Keith¹¹). This finding in a person of twenty-five years with normal caliber of arterioles in the organ distal to the coarctation, in the absence of other obvious etiology, would suggest that the hypertension was possibly a factor in its production. The thickening of the coronary arteries and arterioles may possibly be the result of the high blood pressure existing above the point of coarctation, although the evidence presented is admittedly too inconclusive to justify a definite causal relationship. Unfortunately the arterioles of other tissues above the site of coarctation were not studied from this standpoint. If this

hypertension was productive of these arterial changes, it is conceivable that its longer duration would result in more definite sclerotic lesions. In spite of the high systolic pressure above the point of coarctation and a lower pressure below, there is no conclusive evidence that sclerotic changes in the vessels are more marked above the point of constriction. Occasionally the vessels below the point of coarctation have shown more sclerosis than those above.¹⁶

In Hamilton and Abbott's⁹ latest series of 200 cases of coarctation there were but 33 in which rupture of the aorta occurred proximal to the point of coarctation. In two cases, rupture of the heart itself occurred, and in five rupture of the aorta was below the point of coarctation. In the great majority of their series, this tear, as in our case, led to a dissecting aneurysm which extended from between the layers of the media or the media and adventitia, and ruptured secondarily hours or days after the primary intimal tear. There were apparently but few cases where the tear occurred through all the coats of the vessel with death following immediately.

A dilatation of the ascending aorta, as was present in our case, was observed in 101 out of the 200 cases of their series; in 71 this point was not mentioned. Cardiac hypertrophy, especially of the left ventricle, is extremely common and was noted in 150 of their cases. However, cardiac hypertrophy was not necessarily present and was absent in some of the older patients. In 108 of their series the stenosis resembled or approached that observed in our case; i.e., the opening was reduced to a very small lumen ranging in diameter from 6 mm. to one so minute as to allow the passage of a hair or bristle. In 47 of the 200 cases the stenosis was complete. It is interesting to note the causes of death in coarctation. Spontaneous rupture of the aorta or heart occurred in 40 cases; 24 patients died from a cerebral lesion, usually hemorrhage; 60 from cardiac decompensation and 17 without apparent cause.

SUMMARY

A case of coarctation occurring in an apparently healthy young adult is reported in which death was due to rupture of the aorta.

The possible relation of hypertension to arteriosclerosis is discussed.

REFERENCES

1. Blackford, L. M.: *Arch. Int. Med.* 41: 702, 1928.
2. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C.: *Arch. Int. Med.* 47: 806, 1931.
3. East, T.: *Proc. Roy. Soc. Med.* 25: 796, 1932.
4. Eppinger, E. C., and Midelfart, P. A. H.: *Am. J. M. Sc.* 185: 528, 1933.
5. Ernstene, A. C., and Robins, S. A.: *Am. J. Roentgenol. & Rad. Therap.* 25: 243, 1931.
6. Evans, W.: *Quart. J. Med.* 2: 1, 1933.
7. Fishberg, A. M.: *Arch. Int. Med.* 35: 650, 1925.
8. Fray, W. N.: *Am. J. Roentgenol. & Rad. Therap.* 24: 349, 1930.

9. Hamilton, W. F., and Abbott, M. E.: AM. HEART J. 3: 381, 1928.
10. Hampson, A. C.: Proc. Roy. Soc. Med. 25: 420, 1932.
11. Kernohan, J. W., Anderson, E. W., and Keith, N. M.: Arch. Int. Med. 44: 395, 1929.
12. King, J. T.: Arch. Int. Med. 38: 69, 1926.
13. Lemon, W. S.: Tr. Assn. Am. Phys. 46: 340, 1931.
14. Railsback, O. C., and Dock, W.: Radiology 12: 58, 1929.
15. Rösler, H.: Wien. Arch. f. inn. Med. 15: 521, 1928.
16. Thomson, A. P., and Lamb, F. W. M.: Arch. Dis. Child. 4: 377, 1929.
17. Ulrich, H. L.: AM. HEART J. 7: 641, 1932.
18. Woltman, H. W., and Shelden, W. D.: Arch. Neurol. & Psych. 17: 303, 1927.

SCLEROSIS OF THE CORONARY ARTERIES WITH MYOCARDIAL INFARCTION IN A YOUNG WOMAN

H. W. RATHE, M.D.

WAVERLY, IOWA

ARTERIOSCLEROTIC heart disease in men under forty years of age has been mentioned in the literature on numerous occasions, but the condition is apparently rarely encountered in women of this age period. Levine¹ in his monograph reported three young adults, one of whom was a woman thirty-nine years old. Willius and Brown² describe the case of a woman thirty-five years of age with angina pectoris and myocardial failure, who died suddenly. Although a necropsy was not performed, the clinical manifestations justified the diagnosis of coronary artery disease. Wolff and White³ cite a case from the literature of a young woman twenty-one years of age in whom a diagnosis of coronary artery disease was confirmed by necropsy.

The following case report concerns a woman who at the onset of her symptoms was thirty-two years old. When she was first seen, it was felt that a sclerosis of the coronary vessels was probably responsible for her cardiac disability. The age of the individual, the presence of a nodular goiter and the subsequent course suggesting infection, however, made this diagnosis uncertain.

CASE REPORT

Mrs. J. R. M., white, aged thirty-three years, was admitted to the hospital for examination October 27, 1932.

History.—She complained of nervousness, weakness, shortness of breath on exertion, attacks of choking sensation during the night, and cough.

The onset of the symptoms dated back to about two months prior to the birth of her last child in April, 1932. At this time she noted that she became unusually short of breath on exertion. The labor was normal, and following this there were no particular complaints until July of the same year. She began to experience shortness of breath on exertion, became fatigued easily, and in a short time became very nervous. These symptoms gradually progressed, and in September nocturnal dyspnea appeared. The latter was described as attacks of choking sensation which would awaken her from sleep and compel her to sit up in bed to get her breath. When first seen about one month later she complained chiefly of the dyspnea and a nonproductive cough. The nocturnal attacks gradually increased in frequency and in severity. There was no history of pain suggestive of the anginal type. She stated she had lost about 30 pounds in weight during the past four months, the present weight being 176 pounds.

She apparently had not been strong as a child, but according to her history had had no significant illness aside from a severe attack of scarlet fever at twenty-two years of age. She was not aware of any cardiac involvement from the scarlet fever. A careful inquiry was made concerning rheumatic infection, and with the possible

exception of growing pains at the age of twelve years, the history from this standpoint was negative. She was married at twenty-three years and weighed 125 pounds. Six months after the birth of her first child her weight had increased to 170 pounds. She had two children who were living and well and had had no miscarriages. Both pregnancies were carefully followed, and at no time was there any elevation of the blood pressure.

The father and mother, two brothers and two sisters were alive and well. On the paternal side there was a history of several cousins having died from heart disease, but the basis of the cardiac disability was not known.

Findings.—The patient was moderately obese and well developed. Pupils reacted promptly to light and accommodation. There was a moderate sclerosis of the retinal vessels. The teeth appeared to be in good condition and except for an enlargement of the right tonsil nothing of particular importance was noted in the examination of the nose and throat. There was a moderate nodular enlargement of the thyroid gland. The lungs were apparently clear. In the examination of the heart the muffled cardiac tones and the gallop rhythm were the most conspicuous features. The left border of the heart was just outside the midclavicular line and there were no definite murmurs. The systolic blood pressure was 119 mm. and the diastolic 92 mm. The pulse was of the low tension type, and there were no significant alterations in the walls of the peripheral vessels. The liver was enlarged, extending a hand'sbreadth below the costal margin and was moderately tender. There was no peripheral edema. The blood picture was that of a mild secondary anemia and the urine was negative. In the teleroentgenogram the transverse diameter of the heart was 16.5 cm. and the transverse thoracic diameter was 28 cm. The blood Wassermann was negative. The basal metabolic rate was minus 10 per cent.

Clinical Course.—In spite of periods of absolute bed rest, promotion of relaxation and sleep and various additional therapeutic measures, the clinical course was progressively downward. The dyspnea became a very prominent feature with distressing periods of orthopnea, and in time anasarca developed. There was no particular alteration in the blood pressure, and the cardiac rhythm was regular except for an occasional auricular and ventricular premature contraction. The heart sounds gradually became distant and the gallop rhythm more conspicuous. The electrocardiogram taken at the time of the first examination presented a left axis deviation with a slight slurring and some increase in the duration of the QRS complex. Later there was a gradual reduction in the amplitude of the chief ventricular deflection. The patient died March 3, 1933.

Pathological Report.—(The autopsy was limited to the examination of the heart.) The heart weighed 400 gm. There was a rather extensive dilatation of the left ventricle with a mural thrombus in the left ventricle and right auricle. The myocardium presented a moderate degree of fibrosis involving particularly the subendocardial layers of the left ventricle. The changes in the coronary arteries involved particularly the smaller branches as shown in the microscopic sections.

Histological examination: Sections were taken from the anterior wall of the left ventricle, apex of the left ventricle, the interventricular septum and the right auricle. In the section from the anterior wall of the left ventricle there was an absence of the cross striations of the subendocardial muscle cells, and these fibers were swollen and stained pale blue. One area of the endocardium showed an adherent and partially organized thrombus. Several small areas of infarction, acute, subacute and old were seen. Over the entire section the muscle fibers appeared somewhat atrophic and the vessels were thickened. Two of these vessels showed partially organized thrombi. In the section taken from the apex of the left ventricle the mural thrombus was considerably thicker than that presented in the above section. The cardiac musculature likewise showed varying degrees of degen-

eration. In the section from the interventricular septum there was a rather extensive degeneration of the muscle cells with young fibrous tissue proliferation. The section from the right auricle was composed largely of organized thrombus. The auricular muscle stained poorly and showed some vacuolization.

COMMENT

The above case report is that of a young woman in whom the clinical diagnosis of probable coronary artery disease was verified by necropsy. The histological examination showed extensive degenerative changes in the myocardium, secondary to sclerosis and occlusion of certain of the smaller coronary vessels.

While sclerosis of the coronary arteries producing cardiac disability is rare in women of this age, the possibility must be borne in mind, particularly in the absence of other etiological factors. In this patient the presence of a nodular goiter directed attention to the possibility of a thyrotoxicosis, but at no time were there any apparent clinical manifestations of this condition.

Note.—I wish to acknowledge my indebtedness to Dr. J. W. Kernohan of the Department of Pathology, Mayo Clinic, for the pathological report.

REFERENCES

1. Levine, S. A.: Coronary Thrombosis, Various Clinical Features, *Medicine* 8: 245, 1929.
2. Willius, F. A., and Brown, G. E.: Coronary Sclerosis, an Analysis of Eighty-Six Necropsies, *Am. J. M. Sc.* 168: 165, 1924.
3. Wolff, L., and White, P. D.: Acute Coronary Occlusion, *Boston M. & S. J.* 195: 13, 1926.

Correspondence

A PLEA FOR UNIFORMITY IN THE BIOLOGICAL STANDARDIZATION OF COMMERCIAL PREPARATIONS OF DIGITALIS

To the Editor of the American Heart Journal:

The chemistry of the digitalis glucosides is, as yet, but imperfectly understood. Chemical assay is therefore not feasible, and it is necessary to resort to the technic of biological standardization. Most of the digitalis products now marketed in America are so standardized.

The present situation with respect to the biological assay of digitalis is unsatisfactory both to practitioners of medicine and to the manufacturing drug firms. The various factors which lead to confusion are as follows:

1. The one-hour frog method is official in the Pharmacopeia of the United States.

2. Other methods of assay have been devised, and one or another of these is employed for the standardization of commercial products, e.g., the cat method of Hatcher and Brody, the guinea-pig method of Vanderkleed, and the Magnus modification of the Hatcher-Brody technic. The establishment of an international unit has also been attempted, and at least one firm markets a preparation said to be assayed in terms of this unit.

3. There is abundant evidence which indicates that the cat method of Hatcher and Brody yields uniform and reliable results, and that the relative potencies of different preparations, as determined by this method, apply to human dosage. When a specimen is found to be twice as active as another by this method, it is also twice as active in man.

4. No standard of potency has been established for preparations that are assayed by the cat method. Thus, 1 c.c. of a given tincture may contain the equivalent of $\frac{1}{2}$ cat unit; 1 c.c. of another tincture may contain 2 cat units. Tablets, pills and capsules vary in like fashion.

When the physician prescribes digitalis, he is entitled to receive a dependable and uniform product. The drug manufacturer requires, and is anxious for, guidance and support from the medical profession. He is confronted on the one hand by the U. S. Pharmacopeia, which sets its stamp of approval upon the frog unit; and on the other hand, by a majority of competent cardiologists and pharmacologists, who favor the use of the cat unit.

The Heart Committee of the New York Tuberculosis and Health Association has, for a number of years, distributed to its constituent cardiac

clinics tablets of digitalis leaf standardized by the cat method of Hatcher and Brody. The tablets have been made up to the strength of one cat unit, one-half cat unit, and two cat units. The experience with this preparation has been entirely satisfactory.

On the basis of the facts cited, the following recommendations are made by the Heart Committee of the New York Tuberculosis and Health Association:

1. For the present, and until further knowledge may necessitate a change in point of view, digitalis preparations should be standardized by the cat method of Hatcher and Brody. For convenience the exact procedure now followed in Dr. Hatcher's laboratory is appended.

2. In marketing commercial products, liquid preparations of digitalis should be put up so that 1 c.c. (15 minims) contains the equivalent of 1 cat unit.

3. In marketing tablets, pills or capsules of digitalis, each of these should contain the equivalent of 1 cat unit. Tablets, pills or capsules containing stated fractions or multiples of 1 cat unit may be dispensed, if desired.

It is hoped that the manufacturing drug firms will adopt these simple suggestions, for by so doing they will be rendering a real service to the members of the medical profession and their patients.

These recommendations have been approved by the Executive Committee of the American Heart Association.

APPENDIX

The cat method of Hatcher and Brody, as carried out in the Department of Pharmacology of the Cornell University Medical College, is as follows:

The digitalis leaf to be assayed is first made up into a tincture, in accordance with the directions given in the U. S. Pharmacopeia. The tincture is then diluted twenty times with physiological salt solution. The diluted tincture is injected slowly and continuously from a burette into the saphenous vein of the cat until death results from ventricular fibrillation. The rate of injection is such that the total dose is injected in about ninety minutes. The test may be made during light ether anesthesia; or only local anesthesia may be employed, 1 per cent novocaine being injected or 10 per cent phenol being rubbed into the skin for the exposure of the vein. Six cats are usually employed for one test. Pregnant, lactating or excessively fat animals are not used.

The cat unit potency of the preparation is the average of the results obtained with the group of animals and is expressed as the volume, in cubic centimeters, of undiluted tincture per kilogram of the animal required to cause death under the conditions described. The amount of leaf contained in this unit of tincture is readily calculated.

(Signed) Digitalis Committee.

Ernst P. Boas

Alfred E. Cohn

Arthur C. de Graff

Cary Eggleston

Harry Gold

Bernard S. Oppenheimer

Robert L. Levy, Chairman.

Harold E. B. Pardee

Homer F. Swift

John Wyckoff

Department of Reviews and Abstracts

Selected Abstracts

Clawson, B. J.: Relation of Allergy to General Resistance in Streptococcic Infection. *J. Infect. Dis.* 53: 157, 1933.

A study of the relation of allergy to resistance was made in two series of animals. One group was rendered hypersensitive to streptococci, the other was made highly resistant to streptococci without the allergic state developing. The rate at which living streptococci were removed from the blood and liver following intravenous injections was compared in these two series and in normal animals. The height of the streptococcic agglutination titer was also compared in the three series of animals. It was found that organisms were not removed from the blood stream as rapidly in fifteen minutes in the allergic animals as in the normal animals. This suggested some harmful factor associated with the phenomenon of allergy. After two hours, however, a greater number of streptococci per gram of liver were killed in the allergic animals than in the normal animals. This difference was but a slight one. On the other hand, in the animals which were made resistant without allergy developing, organisms in the blood stream and in the liver were killed at a much greater rate than they were in either the normal or the allergic animals.

The findings in the experiments suggest that the allergic state is not necessary in the development of general protective resistance to streptococci. It even seems that allergy may be harmful from the standpoint of its effect on the phagocytic cells. It should not be said, probably, that allergy in general is a harmful concomitant phenomenon associated with resistance, for, from the standpoint of repair of tissues, allergy might be looked on as being useful, since the growth of connective tissue is stimulated. In the light of the foregoing experiments, it would seem that allergy bears no useful relation to general resistance in streptococcic infection, as indicated by phagocytosis, and that at times there may be a harmful relation.

Griffith, George C., Chamberlain, C. T., and Kitchell, J. R.: A Simplified Apparatus for Direct Venous Pressure Determination Modified From Moritz and V. Tabora. *Am. J. M. Sc.* 187: 371, 1934.

A simple and inexpensive apparatus for venous pressure determination by the direct method of Moritz and v. Tabora is described together with the technic for its use. Attention is directed to the importance of estimating venous pressure in the diagnosis and treatment of cardiovascular disease.

Eyster, J. A. E., and Hicks, Earl V.: Effect of Respiration on Cardiac Output. *Am. J. Physiol.* 104: 358, 1933.

In dogs under anesthesia in which stroke volume and minute cardiac output from the two ventricles is measured by a cardiometer during normal breathing, there occur during inspiration a diminished stroke volume and a slight fall of

right auricular pressure. The effective venous pressure is increased, since the fall in auricular pressure is not so great as the fall in intrathoracic pressure. The diminished total stroke volume may be explained by diminished left ventricular output due to retention of blood in the increased pulmonary bed.

In the greater reduction of intrathoracic pressure associated with the deep inspirations following vagus section, these effects are exaggerated, and in addition the diastolic volume is increased.

Under the conditions of these experiments, marked alterations of breathing have little effect on the average stroke volume or on minute volume when considered over a period of time. It is believed that the influence of the extent of breathing on venous return is not so great as is ordinarily stated.

Brams, W. A., Katz, L. H., and Kohn, L.: The Effect of Abdominal Distention and Release on the Blood Pressures in the Arteries and Veins. Am. J. Physiol. 104: 120, 1933.

The effects of induction and release of abdominal distention on venous pressure, arterial pressure and cardiac stroke volume were studied in a series of 51 experiments.

The pressure in the inferior vena cava rose when the abdomen was distended while the pressure in the superior vena cava was slightly elevated or but little affected. Release of distention resulted in a prompt return of pressure in the inferior vena cava to normal. These results were approximately the same in experiments of short and long duration and in instances where distention was maintained for several days.

Arterial pressure fell in 27 of 48 experiments during distention of the abdomen and rose in 21 others. In 34 experiments a fall to a level below the normal occurred on abrupt release of abdominal distention. This was mirrored in the changes in stroke volume. The interplay of various factors responsible for these changes is discussed.

On release of distention of the abdomen a fall of arterial blood pressure was usually obtained. The fall in arterial pressure was 40 mm. of mercury in some instances and was sustained at that low level in a few.

The clinical importance of such a fall in arterial pressure on release of distention as a cause of syncope and death is discussed and adrenalin suggested as a rational form of treatment in the emergency.

Gregg, D. E., and Wiggers, C. J.: The Circulatory Effects of Acute Experimental Hypervolemia. Am. J. Physiol. 104: 423, 1933.

The plasma and erythrocyte volumes of anesthetized dogs were increased experimentally by slow infusion of sedimented corpuscles during which pressure changes in the veins, ventricles and central arteries were followed, the latter two by use of optical manometers with a high figure of merit. In addition, alterations in urinary secretion, spleen volume, intrathoracic pressure, etc., were incidentally recorded.

The experiments demonstrated the following points: (1) While a considerable volume of blood can be accommodated by the dilatation of capillaries and venules in various blood reservoirs of the body, including the spleen, the maximum capacity available under normal conditions is not adequate to prevent an increased return to the heart during polycythemic hypervolemia. (2) The heart enclosed by its pericardium within the closed chest does not differ in its response from that of an exposed heart up to the limits imposed by very large increases in blood volumes. Evidence that the systolic discharge of the left ventricle increases is

given by the larger pulse pressure, the inordinate increase in the phases of isometric contraction and systolic ejection as well as by the contour changes exhibited by the pressure pulses. These are discussed. (3) Intraventricular pressure curves obtained from exposed hearts enclosed naturally within the pericardium indicate that initial tension increases considerably, thus supplying the force by which dilatation up to the capacity of the pericardial sac can be produced. The increased initial tension and length therefore represent the coefficients which determine the steeper gradient of the ventricular pressure pulses and the prolongation of systole. (4) During the early stages of hypervolemia, the increased systolic output is mainly responsible for the elevation of arterial pressure, for the gradients of the diastolic portion of the pressure curves do not change. This indicates that the increase in peripheral resistance occasioned by greater blood viscosity is nicely counterbalanced by dilatation of peripheral arterioles and widening of the capillary beds. These experiments supply no information as to whether this involves active changes in the caliber of peripheral vessels or is entirely passive. When the polycythemic hypervolemia becomes extreme, however, the effects of increased viscosity dominate and an increased peripheral resistance undoubtedly occurs. This is shown by the changing contour of the systolic portion of the pressure pulses and by a slower gradient of the diastolic decline as well.

Parkinson, John: The Radiology of Heart Disease. Brit. M. J. 2: 591, 1933.

In the modern diagnosis of cardiovascular disease, radiology takes an essential and important place comparable with that of electrocardiography. Radiology, when available, replaces percussion, for it is more accurate and informing and thus contributes to the progress of cardiology. Examination of a patient with doubtful or serious cardiac disease is incomplete unless it includes radiological examination. Diagnosis is confirmed and extended, and prognosis may be affected.

An anterior film alone is often inadequate. Radioscopy in the anterior and both oblique positions should be followed where necessary by telerradiograms in the anterior and left oblique, with or without the right oblique. Enlargement of the heart should not be diagnosed in the absence of an adequate cause and converging evidence unless radiological confirmation is obtained. Apparent enlargement is not infrequently due to scoliosis.

The difficulties surrounding the radiology of heart disease largely disappear if instead of looking for general enlargement, attention is centered upon the particular chambers or great vessels which may be modified in size, shape, or position.

Special care should be taken not to distress a patient by confronting him with x-ray findings as if they implied an additional diagnosis or a complication which magnified his disease.

Kerley, Peter: Radiology in Heart Disease. Brit. M. J. 2: 594, 1933.

This article describes briefly the technic of radiology of the heart and the findings in both normal hearts and those which are either small, enlarged, or which show changes in shape due to valve disease. The author also describes the findings in the lung due to hyperemia, edema and collapse, associated with heart disease.

Bramwell, Crighton: Radiological Diagnosis of Cardiac Enlargement. Brit. M. J. 2: 597, 1933.

The author believes that x-ray examination makes three important contributions to the diagnosis of pathological cardiac enlargement.

It can tell us all that we can learn from percussion and palpation regarding cardiac enlargement, and it can do so with a much higher degree of accuracy than either of these methods.

It can give us reliable information regarding slight changes in heart size and the slighter degrees of cardiac enlargement, even under the most unfavorable circumstances. Although slight cardiac enlargement by itself is not sufficient ground on which to base a diagnosis of heart disease, it may sway the balance when considered in conjunction with evidence from other sources.

X-ray examination can reveal changes in the shape of the heart outline. These changes tell us which chambers are enlarged and so indicate the probable cause of the enlargement. This is the most important contribution. The frontal silhouette alone gives us a far more accurate idea than does percussion of the shape of the heart, whereas examination in the two oblique positions yields additional information of which percussion can tell us little or nothing.

Rosenthal, Maurice: *An Anatomic Mechanism in the Production of the Flint Murmur.* Arch. Path. 16: 862, 1933.

Two cases are presented in which a definite organic lesion not involving primarily the mitral valve seem to offer a definite and concrete explanation for the Flint murmur that was observed during the life of these two persons. Although the original and the previously given modified explanations of the mechanism of the Flint phenomenon are possible, they are not based on demonstrable pathological and anatomical changes; and this fact, associated with the vagueness of the clinical definition of the murmur, greatly weakens the value of this phenomenon for the clinician. If only one type of this murmur, therefore, can be established as caused by variation in anatomical structure, it would seem that it can be definitely removed from the group of poorly understood functional murmurs and included in that of the important organic murmurs of morphological significance. It is believed that one cause of the Flint murmur is a mechanical deformity or distortion of an otherwise essentially normal anterior flap of the mitral valve.

The deformity consists of a bulging of the anterior mitral leaflet with the formation of a culdesac on the auricular surface. This may be produced by vegetation on the posterior aortic cusp or by a calcified posterior cusp stiffened and fixed in its diastolic phase. Various aortic diseases may produce this deformity, such as bacterial infection, active or healed, arteriosclerosis and occasionally syphilis of the aorta, if it is complicated by secondary involvement and sclerosis of the aortic cusps.

Mackinnon, A. U.: *The Rhythm of Paroxysmal Tachycardia. An Electrocardiographic Study.* Quart. J. Med. 3: 1, 1934.

The common type of paroxysmal ventricular tachycardia is markedly regular, and such irregularities as are present between consecutive beats are so slight as not to be appreciable by the human ear as departures from a regular rhythm.

Certain cases of auricular paroxysmal tachycardia may be clinically irregular. In the absence of the so-called Gallvardin's sign—the presence of a venous wave in the neck beating at a definitely slower rate than the ventricle—clinical irregularity in a typical paroxysmal tachycardia should not be held to indicate the presence of a ventricular origin until the electrocardiogram has proved the diagnosis beyond dispute.

As a general rule cases of auricular paroxysmal tachycardia have a greater degree of regularity than those tachycardias arising in the ventricle.

Irregularity in paroxysmal ventricular tachycardia may be due to: (1) con-

duction disturbances between focus and ventricle; (2) focal stimuli being too weak to excite the ventricle, or ventricular excitability so diminished that the ventricle does not respond to normal stimuli; (3) stimuli arising irregularly from a single focus; (4) stimuli arising irregularly from more than one focus in the ventricle.

Mohler, Henry K., and Crawford, Baxter L.: The Pathologic Changes in the Heart in Auricular Fibrillation. Am. J. M. Sc. 187: 171, 1934.

The hearts of 15 fibrillators and 7 nonfibrillators having an etiology of rheumatic fever and mitral valve lesions were studied pathologically.

The hearts of 9 fibrillators with arteriosclerosis as the etiological factor were also studied. They had sclerotic changes in mitral valves in 7 with apparently normal valves in 2 cases.

There were no pathological changes common to all cases of auricular fibrillation found in this series of hearts. Nothing in this investigation indicates that the type of pathological lesion found at autopsy can of itself be responsible for the onset and continuation of auricular fibrillation. Etiological factors apparently determine the type of pathological changes to be found in the heart to a greater extent than does the presence or absence of fibrillation.

King, John T.: Bundle Branch Block. Am. J. M. Sc. 187: 149, 1934.

An analysis of 155 instances of bundle-branch block in 150 patients is reported. In 17 cases in which autopsies were obtained a close correlation between clinical and pathological diagnoses was found. No attempt was made to determine the exact site of the lesion.

Most instances of bundle-branch block occur in association with degenerative heart disease; though a smaller number are found with about equal frequency in syphilitic or rheumatic infections of the heart. The proportion of cases is somewhat higher in general in rheumatic subjects than in syphilitic. Laborers are more prone to develop bundle-branch block than are professional men or housewives, while business men are neither predisposed nor immune. The condition is more common among men than among women.

In order of incidence, the important pathological disorders of cardiac mechanism may be listed as follows: auricular fibrillation, bundle-branch block, auriculo-ventricular heart-block, auricular flutter. First degree heart-block and complete A-V dissociation are found commonly associated with bundle-branch block. Bundle-branch block should be considered one of the rather common as well as important clinical entities. Various auscultatory phenomena encountered in bundle-branch block are recorded in diagrammatic form. It is emphasized that such signs are of less aid in establishing a diagnosis based on physical signs than are the surface movements of the cardiac apex.

The prognosis is very grave regardless of the etiology, though it appears best in those cases of rheumatic etiology. The occurrence of bundle-branch block seems to add nothing to the gravity of the prognosis of syphilitic heart disease. Since some individuals live for a considerable period with bundle-branch block, perhaps its presence should be looked upon as an omen of very grave import rather than as a necessarily fatal handicap.

Maher, C. C., Sullivan, C. P., and Scheribel, C. P.: The Effect Upon the Electrocardiograms of Patients With Regular Sinus Mechanism of Quinidin Sulphate. Am. J. M. Sc. 187: 23, 1934.

Quinidine sulphate was administered to 19 patients with no general toxic effects. The electrocardiograms in the majority of these patients showed changes only

in regard to the T-wave within from twenty-four to seventy-two hours if orally administered and immediately if given intravenously. These changes varied from mild flattening to sharp inversion of the T-waves. The duration of the effect varied from three to six days on oral administration and three hours on intravenous administration. Changes in the QRS and P-R intervals are presumably effects produced by intoxicating doses.

Gold, Harry, and Klumpp, Margaret M.: On the Alleged Antagonism Between Digitalis and Diphtheria Toxin. *Am. J. M. Sc.* 185: 509, 1933.

Results of this study show that digitalis does not afford any protection against poisoning by diphtheria toxin in the cat. It is probable that the same is true in man. It was also observed that very large doses of digitalis may hasten the death of animals poisoned by diphtheria toxin. Reference also is made to the fact that the routine use of digitalis in pneumonia does not lessen the mortality from that disease.

Evans, William, and Hoyle, Clifford: The Prevention and Treatment of Individual Attacks of Angina Pectoris (Angina of Effort). *Quart. J. Med.* 3: 105, 1934.

A series of 122 patients with angina pectoris was observed over a period of three years with special reference to the comparative value of vasodilator drugs for the immediate treatment and prevention of attacks. The comparative results show that glyceryl trinitrate in tablet form when absorbed from the mouth is by far the most effective agent for relieving attacks and for their immediate prevention. Eighty-six per cent of the patients obtained great relief and a further 11 per cent moderate relief. Other preparations of glyceryl trinitrate and other remedies tried did not give such good results. Glyceryl trinitrate tablets should deservedly hold the first place in routine treatment. This is more advisable because they rarely cause objectionable symptoms; they are easy to store and carry so that they are always available for immediate use, and they are cheap. The only practical disadvantage is that they deteriorate in strength, especially when exposed to air and heat, so that they should be used preferably within two months of manufacture. Amyl nitrite proved to be disappointing for the relief of attacks, and it can be recommended only for those rare cases where glyceryl nitrate fails to relieve. It has the further disadvantage of being useless for the prevention of attacks.

The use of glyceryl trinitrate tablets immediately before expected anginal attacks is a safe means of preventing pain and should be used far more widely in routine treatment than it is at present. In our series 84.5 per cent patients obtained great benefit and a further 12.5 per cent moderate benefit by using the drug in this way. This is a greater measure of improvement than was found from any of the remedies tried in this investigation of continuous treatment. Most patients preferred to take the drug at their own discretion, and this method of administration proved more effective than when it was taken at short fixed intervals, except for those patients who could not predict attacks with certainty. No harmful effects were met from such treatment; though patients used the drug freely for upwards of two to three years, and often this enabled them to take more physical exertion and lead a fuller life than had previously been possible.

Gilchrist, A. Rae: The Action of Atropine in Complete Heart Block. *Quart. J. Med.* 2: 483, 1933.

The response of ten individuals suffering from complete heart-block has been tested by the intravenous administration of $\frac{1}{40}$ gr. of atropine sulphate. Re-

peated electrocardiograms taken at intervals before and after the injection demonstrated that in every case studied this drug produced an acceleration of the ventricular rate.

The prevailing view, constantly repeated in the literature, that atropine has little or no effect on the frequency of the ventricles is incorrect and requires modification in the light of the peculiar character of the acceleration. The dose of atropine was sufficient to produce almost complete paralysis of the vagus. The maximum increase in ventricular rate was 47 beats per minute, representing a gain of almost 96 per cent over the initial rate. The minimum acceleration was 1.2 beats per minute, giving a percentage increase of 5.4. In only one case was the gain after atropine within the maximum range recorded under similar resting conditions.

The initial ventricular rate is the important factor in determining the amount of acceleration for a given dose of atropine, the higher the resting rate the greater the response to atropine. At low initial rates atropine produces but little acceleration. The coefficient of correlation between the rate before atropine and the amount of ventricular acceleration produced by it is +0.97—a very significant relationship.

The law expressing the degree of acceleration for a given initial ventricular rate has been represented by a straight-line formula. Actually, this is probably not the best expression. It would appear from the available data that a logarithmic curve might be the best expression, but the facts are too scanty to allow of its exact determination.

The use of atropine as a means of distinguishing the bradycardia of complete heart-block from other causes is therefore unreliable. Further work requires to be done on this subject with the object of determining the precise nature of the response to atropine in those cases of slow heart action in which complete heart-block is not present.

To obtain a decided effect on the ventricular rate, it is necessary to use an amount of atropine approaching the full paralyzing dose; $\frac{1}{30}$ gr. of atropine given intravenously in 1 c.c. of normal saline was found to be sufficient.

In contrast to the ventricular response, the auricular acceleration does not appear to bear any relation to the initial auricular rate. Further, the auricular range after atropine does not bear any relation to the ventricular. The amount of auricular acceleration varies irregularly from individual to individual. The auricular response probably reflects no more than the degree of vagal tone existing at the moment of injection.

The nature of the ventricular response suggests that the amount of acceleration is determined by the inherent rhythmicity of the specialized tissue at the center of impulse production. It is suggested that when the lesion producing the block is situated in the uppermost part of the conducting tract, a greater response will occur after atropinization than when the center of impulse production lies at a lower level in the specialized tissues.

As a converse of this, it may be suggested that vagal stimulation is more likely to be effective in slowing the idioventricular rate when the center of impulse production lies high in the conducting tract.

Gilchrist, A. Rae: *The Action of Adrenalin in Complete Heart Block*. Quart. J. Med. 2: 499, 1933.

Twelve cases of complete heart-block have been tested with repeated subcutaneous doses of adrenalin in an attempt to discover the factors which govern the response of the heart to this drug.

After a subcutaneous dose the drug comes into action with surprising rapidity. Acceleration of auricles and ventricles may occur within from two to four minutes of the injection.

The amount of ventricular acceleration induced bears a striking relationship to the rate existing immediately before the injection. High initial rates are followed by little or no gain in rate, slow rates by pronounced acceleration. This means that the state of the heart at the time of the drug's administration determined the heart's response.

By plotting the observed increment against the corresponding initial rate, it is found that for a group of eight cases the reaction approximates to an almost perfect series of decreasing exponentials for increasing ventricular rates.

Within a certain range of dosage, the amount of adrenalin injected makes little or no difference to the ventricular response at a given ventricular rate. The optimum response to 0.5 c.c. adrenalin for various initial rates has been calculated and compared with the reaction observed after doses of 0.25, 0.75 and 1.0 c.c. in the same subjects. The gain in rate after these doses is to all intents similar to that recorded after 0.5 c.c. This implies that the response of the heart is determined, not by the size of a dose in the usual therapeutic range but by the rate of the heart existing at the time of the injection. In other words, for a given initial rate 0.25 c.c. of adrenalin will produce as much acceleration as a dose four times that amount.

This phenomenon is discussed in the light of the known laws which govern enzyme action. The independence of the size of the dose and the response recorded, suggests that a surface action is involved and that adrenalin is being absorbed on some (? enzyme) surface, as an essential condition of its action.

The observation that the initial rate determines the degree of acceleration finds support in blood pressure studies. Lyon has suggested that the reaction to adrenalin obeys Weber's law, in that the amount of elevation in the systolic blood pressure after uniform doses of adrenalin depended upon its level at the moment of the injection.

It has not been found possible to demonstrate as close a correlation between the initial auricular rate and its increment after adrenalin as that observed in the case of the ventricles. The auricular response is modified to some extent, particularly in those cases in which the magnitude of the ventricular response is maximum, that is, when the initial ventricular rate is relatively low.

It would appear probable that reflex vagal influences, induced by a marked ventricular reaction, limit the auricular response. The amount of limitation is apparently determined largely by the initial ventricular rate.

The course of the reaction to a subcutaneous dose of adrenalin varies as much in complete block as it does in the normal beating heart. The maximum auricular and ventricular reactions are not necessarily synchronous. As a general rule the auricles attain to the height of their reaction before the ventricles have completed their acceleration. An increased frequency of both chambers of the heart persists after the blood pressure rise has returned to its preexisting level. No untoward symptoms resulted from the use of the drug. Release from the block was not observed in any of the experiments performed upon these eight patients.

Reactions differing from those just described were encountered in four patients. One of these cases was a man who suffered from intermittent complete block. Tested with adrenalin during complete block, no change in the rhythm occurred, but a branch defect changed from one side of the heart to the other.

Tested during two-to-one rhythm, complete block was induced. The direction of the main ventricular deflection varied according to the presence or absence of conduction through the main stem of the bundle. During half rhythm the ventricular complex in Lead III was directed downward, whereas during complete dissociation its direction was upward. The fact that this man's heart was unduly susceptible to adrenalin suggests that in cases of intermittent complete heart-block, the temporary failure of conduction, leading to transient complete dissociation, may perhaps be associated with the formation within the body of some subtle and complex chemical substance analogous to adrenalin or adenosine.

Hitchcock, Charles H., Camero, Anthony R., and Swift, Homer F.: Perivascular Reactions in Lung and Liver Following Intravenous Injection of Streptococci Into Previously Sensitized Animals. *J. Exper. Med.* 59: 283, 1934.

Intravenous inoculation of small doses of nonhemolytic streptococci into previously sensitized rabbits is usually followed by the appearance of perivascular cellular aggregates in lung and liver. The characteristic cell in these aggregates is moderately large with vesicular nucleus, prominent nucleoli, clumped chromatin and basophilic cytoplasm. These characteristics together with the additional evidence of phagocytosis all indicate that the cell probably has its source in the reticuloendothelial system. Further study with vital staining methods and observations of its behavior toward parenterally introduced India ink should furnish more conclusive evidence as to its identity. Whether it is produced directly by the presence of the bacteria or secondarily to the destruction of some other cells or tissue is also a problem for the future to unfold. In addition, the lesions contain small lymphocytes and granulocytes.

This lesion is easily differentiated by architecture and cell content from normally occurring lymphoid aggregates and from spontaneous rabbit hepatic cirrhosis. This mononuclear response does not occur when the intravenous dose is large enough to cause death of the animal within twenty-four hours.

In spleen and lymph nodes the characteristic basophilic cells which normally occur in these organs are present in increased numbers.

Following intravenous treatment alone, or sensitization without intravenous treatment, the lesions occur much less frequently and when present are smaller and more sparsely found.

Inasmuch as in the present series of experiments this lesion was not found in normal animals and infrequently in those treated by the intravenous route alone, it is suggested that the preliminary sensitization serves to enhance the animal's reactivity to the antigen. In this way a small dose of bacteria is capable of eliciting the cellular phenomenon which in unsensitized animals appears only when larger doses of antigen are administered over longer periods of time. Too large a dose of antigen, however, results in shock and cell death rather than in proliferation.

Dawson, M. H.: A Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis. *J. Exper. Med.* 57: 845, 1933.

The present communication presents a detailed study of the subcutaneous nodules in rheumatic fever and rheumatoid arthritis. It is believed that the study has shown that these lesions are highly characteristic of the two diseases and they represent different phases of the same fundamental, pathological process. It is probable that the two diseases represent different responses of affected individuals to the same etiological agent.

Keefer, Chester S.; Parker, Frederic, Jr.; Myers, Walter K.; and Irwin, Ralph L.: Relationship Between Anatomic Changes in Knee Joint With Advancing Age and Degenerative Arthritis. *Arch. Int. Med.* 53: 325, 1934.

In a study of 100 knee joints from 77 consecutive patients who died of various diseases the following facts were determined:

Anatomical changes were noted with increasing frequency with advancing age.

The patella showed alterations in 81 per cent of the cases, the interpatellar groove in 65 per cent, the lateral condyle of the tibia in 64 per cent, the medial condyle of the tibia in 55 per cent, the medial condyle of the femur in 43 per cent, and the lateral condyle in 36 per cent.

The erosions were commonest over the areas of contact which were subjected to the greatest movement, strain, weight-bearing, and injury.

The changes were identical in males and females, and there was no relationship between the extent of the lesions in the joints and the symptoms referable to the joints.

There was no correlation between the lesions in the joints and the degree of arteriosclerosis or any other particular type of disease process.

The gross anatomical changes were indistinguishable from those previously described in degenerative arthritis.

The various factors which are of importance in the development of degenerative arthritis are discussed. They include the aging of tissue, wear and tear, strain, trauma, occupation, and static deformities.

From these observations it seems difficult to escape the conclusion that the changes seen in the joints with increasing frequency with advancing age are identical with those which have been described previously as characteristic of degenerative arthritis. If this is true, there is justification for the belief that degenerative arthritis is a process associated with the aging of the tissues of the joints. This conception is essential for a complete understanding of the pathogenesis of this disorder. Added to the process of involution, such factors as gross trauma, hemorrhage and static deformities exaggerate the condition. The end-result depends upon the summation of these factors.

Weinstein, Israel, and Styron, Norma C.: Bacteriologic Study of Throats in Rheumatic and Nonrheumatic Fever With Special Reference to Hemolytic Streptococci. *Arch. Int. Med.* 53: 453, 1934.

The present investigation includes 321 cases and 840 cultures from Montefiore and Bellevue Hospitals, New York City. Forty-six per cent of the subjects were patients with rheumatic fever. Fifty-eight per cent of the cultures were taken from this group. The remainder were taken from normal persons and from patients suffering from diseases other than rheumatic fever; these constituted the control group. In more than one-third of the cases of rheumatic fever and in more than one-half of the cultures taken from this group the patients were under fifteen years of age.

The percentage of cultures which were positive for the hemolytic streptococcus taken from the throats of patients with rheumatic fever was approximately the same as that found in other persons. In these positive cultures, the hemolytic streptococcus appeared to be no more abundant in those obtained from patients with rheumatic fever than in those from other persons.

Throat cultures of patients with rheumatic fever taken during an infection of the upper respiratory tract showed no greater incidence of hemolytic streptococci than those from other persons who were suffering from a cold or from sore throat.

Infections of the upper respiratory tract were found associated with *Streptococcus hemolyticus* more frequently in young persons who were suffering from rheumatic fever than in older patients with this disease.

Hemolytic streptococci were found more frequently associated with infection of the upper respiratory tract in rheumatic persons who had not had their tonsils removed than in those on whom tonsillectomy had been performed.

Green-producing streptococci were present in all the cases and in 99 per cent of the cultures. They predominated in 69 per cent of the cases and in 73 per cent of the cultures.

Indifferent streptococci were present in 96 per cent of the cases and in 88 per cent of the cultures. They predominated in 3 per cent of the cultures.

In the groups studied, exacerbations of acute rheumatic fever occurred as frequently when there was no infection of the throat as when there was.

The fact that the majority of those in whom exacerbations of rheumatic fever occurred were persons who had hemolytic streptococci in their throats suggests a possible relationship between this organism and the reappearance of the symptoms.

Schlesinger, Bernard, and Signy, A. Gordon: Precipitin Reactions in the Blood of Rheumatic Patients Following Acute Throat Infections. Quart. J. Med. 2: 255, 1933.

Streptococcal precipitins can be demonstrated in the blood of rheumatic patients following acute streptococcal throat infections. Their formation is delayed until from the second to fourth week from the onset of nasopharyngeal infection (the end of the silent period), and their appearance in most cases foreshadows a tendency to a relapse of acute rheumatism.

The precipitin corresponds to the type of streptococcus responsible for the throat infection, but a certain amount of cross precipitin formation may occur. The formation of precipitin is regarded as one of the manifold reactions which take place in the patient's defense mechanism during the silent period. There is thus time for prophylactic measures if the throat infection has not passed unnoticed. Concentrated aspirin therapy during this period undoubtedly prevents serious relapses in many cases. It is not infallible and further research work is urgently required to discover some other method which is still more reliable.

Laws, Clarence L., and Levine, Samuel A.: Clinical Notes on Rheumatic Heart Disease With Special Reference to the Cause of Death. Am. J. M. Sc. 186: 833, 1933.

One hundred and forty-eight cases of rheumatic heart disease were studied to ascertain the cause of death. It was found that congestive heart failure accounted for only 33.1 per cent of the fatalities, acute rheumatic carditis for 23 per cent, peripheral emboli and thromboses for 11.5 per cent, subacute bacterial endocarditis for 29 per cent, and 3.4 per cent of the patients died of miscellaneous cardiovascular accidents like angina pectoris or acute pulmonary edema.

The groups of congestive failure and emboli and thromboses were the oldest, subacute bacterial endocarditis a little younger, and acute rheumatic carditis the youngest.

Those that had aortic valvular disease alone were the oldest (52.5 years). The mitral cases came next (42.8 years) and the cases with combination of aortic, mitral and tricuspid were youngest (39 to 35 years).

There were more than twice as many females as males dying of acute rheumatic carditis, the relation was reversed in the group dying of emboli and

thromboses, and the proportion was three to two on the side of males in the subacute bacterial endocarditis group.

A past history of rheumatic fever or chorea was not found with equal frequency among the various groups. Although the authors believe that stenosis of any of the valves is, except in rare instances of congenital heart disease, practically invariably due to rheumatic infection, the multiform character of the early illness prohibits obtaining a positive history in many instances. The greater the number of valves involved, the more frequently was a positive past history obtained. This is true for two reasons: such patients are more liable to have had more than one infection and they die at a younger age, so that the early illnesses are not forgotten. This explains why patients with aortic stenosis who die at an old age less frequently have a positive past history.

In speaking of valvular lesions in this review, except for those cases dying of subacute bacterial endocarditis, stenosis to a greater or lesser extent is meant. A striking finding was the great frequency of involvement of the aortic and tricuspid valves. When the tricuspid valve was involved, the mitral was always diseased as well, and frequently the aortic.

Auricular fibrillation was almost invariable in the emboli and thrombi group, very common in those dying of congestive heart failure, much less common in the acute rheumatic carditis group and practically absent in those who died of subacute bacterial endocarditis. The presence of mitral stenosis is the most common accompaniment of auricular fibrillation; although this irregularity occurs occasionally in patients who have only aortic stenosis.

The average weight of the heart of those dying with congestive failure was 617 gm., of acute rheumatic carditis or emboli and thromboses about 550 gm., and of subacute bacterial endocarditis 449 gm. The average weight of the heart in cases of aortic stenosis was 669 gm., of mitral stenosis 474 gm., and of both 663 gm. When the tricuspid was involved in combination with other valves, the average weight was about 550 gm. The presence of adhesive pericarditis increased the average weight by about 120 gm. The average weight of 43 cases with adhesive pericarditis was 654 gm., and of 62 cases with a normal pericardium was 534 gm.

Pericarditis with or without adhesions was less frequent in the older patients. It was most common in the group with acute rheumatic carditis, fairly frequent in those with congestive heart failure, and very rare with subacute bacterial endocarditis.

Book Reviews

DISSECTING ANEURYSMS. By T. Shennan. (A report issued by the Medical Research Council.) London. Published by His Majesty's Stationery Office, 1934, 136 pages.

This very complete study of dissecting aneurysms by Professor Shennan of Aberdeen is based upon an analysis of 300 reported cases, including seventeen investigated by the writer himself.

Both the pathological and the clinical features of the condition are discussed fully and interestingly. The author finds that degeneration of the media is a factor common to all cases and that in a majority of instances the media gives way before the intima. Much the commonest cause of death is rupture into the pericardial sac. It is interesting that syphilis seems to play a relatively unimportant etiological rôle in this form of aneurysm.

The monograph includes a historical review of the subject and a full bibliography. It is procurable in this country from the British Library of Information, 270 Madison Avenue, New York City.

L. A. C.

LE DUALISME DE LA CONTRACTION CARDIAQUE. By F. Henrijean. Paris, Masson et Compagnie, 1933, pp. 350.

In this account of the mechanism of heart action, which comprises a full 350 pages, the author gives interpretative analyses, theoretical deductions, numerous tracings of electro- and meehanograms, and a fairly thorough review of a considerable amount of the experimental work in the field.

"The dual mechanism of the cardiac contraction," as announced by the title of the monograph, arouses an expectant interest, but one searches vainly for a concise statement of the real significance of this phrase. The first section of the book is devoted to the electrocardiogram and its relation to certain variations in the contractile response of the heart. In this portion consideration is given to the response of the embryonic heart of the chick, to the action of chloroform, and to the electrical response of the apparently quiescent heart. In each instance the form of the electrical disturbance is discussed in the light of one type of curve which is indicative of the physiological excitatory function of the heart and another which denotes the predominantly energy-transforming phase of cardiac response. Two remaining divisions of the book have to do with interpretations of the form of the electrocardiogram in their bearing on the postulated dual mechanism, and with the rôle played by the vagus and sympathetic nerves in this twofold type of response.

From the standpoint of the essentially new observations in the book it may be questioned whether sufficient warrant is given for all the space devoted to the subject; in fact, much philosophical material might be eliminated without detracting from the main thesis.

D. J. E.

The American Heart Journal

VOL. 9

JUNE, 1934

No. 5

Original Communications

CORONARY ARTERIES IN RHEUMATIC FEVER*†‡

HOWARD T. KARSNER, M.D., AND FRANCIS BAYLESS, M.D.
CLEVELAND, OHIO

INTRODUCTION

THE fact that in the course of infectious diseases lesions of the blood vessels may occur has long been known. Suppurative inflammations may originate in any coat of an artery, due to blood dissemination of bacteria or as the result of direct extension of an inflammation. Less familiar are changes whose origin is uncertain and whose nature is disputed. It is probable that poisonous products of bacteria may produce vascular degeneration. In the case of those diseases now believed to be of allergic nature similar degenerations occur. In the allergic conditions Roessle (1933) has offered the assumption that the vascular lesions are part of a general mesenchymal reaction. There is, however, the possibility that since allergic processes represent antigen-antibody reactions, the meeting of these bodies may occur especially at the junction of blood and tissues in the vessels. This is suggested by the experiments of Apitz (1933) who found that when hemorrhage follows the application of crotalus venom it is due to the meeting at the capillary walls of the venom and the activating substances contained in the circulating blood. The fact that the supposed allergic inflammatory reaction in small arteries occurs especially in media and adventitia is probably explained by the experiments of Ramsey and Alpert (1933) who found that injury of the intima by turpentine or croton oil produces reaction only in the outer media and in the adventitia.

The nature of the process may be clearly degenerative or clearly exudative. In connection with the former, proliferation, especially of con-

*From the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland.

†Aided by a grant from the Josiah Macy, Jr., Foundation.

‡Presented in abstract before the Association of American Physicians, Washington, D. C., May 9, 1933.

nective tissue, occurs; and there is an academic question as to whether this is a substitution process, merely reparative, or a progressive fibrosis of inflammatory nature. It is our view that the proliferation is progressive. Thus the degeneration and proliferation would constitute an alterative type of inflammation.

VASCULAR DISEASE IN GENERAL INFECTIONS

The earlier studies of Hayem (1869, 1870), of Martin (1881, 1883), Huguenin (1883), Landouzy and Siredey (1885, 1887), Therese (1893), Hanot (1894) and others drew attention to acute vascular degeneration, sometimes with endarterial proliferation, in general infectious diseases. The detailed study of the microscopic anatomy was made by Cowan (1904), who described intimal proliferation, round cell infiltration of the media and adventitial fibrosis of coronary arteries in many general infections. Wiesel (1906) laid more emphasis on degenerative changes especially in the media of the coronaries, with serous infiltration and necrosis. He described swelling and rupture of the elastica interna, intimal proliferation, and fibrosis, which he interpreted as scarring. He found that typhoid fever, diphtheria and influenza injured the elastica more severely than did scarlatina and septicopyemic diseases. Wiesner (1906) confirmed these observations and extended them to include eclampsia, endocarditis and congenital syphilis. Frothingham (1911) reported intimal thickening and fat droplets in intima and media in various arteries in general infections.

Wiesel and Loewy (1919) in a study of peripheral arteries in acute and chronic circulatory insufficiency, found coronary lesions only when other peripheral arteries were affected. They attributed the vascular lesions to earlier infectious diseases and were definitely of the opinion that the fibrosis is not inflammatory but reparative and may be accompanied by muscle regeneration. Nevertheless they suggested that the acute arterial disease may be the precursor of arteriosclerosis. Stoerk and Epstein (1920), in their study of the arteries in grip, reported medial changes like those described by Wiesel and Loewy, fatty degeneration of the intima, and sometimes a calcification of fragmented elastica. They emphasized muscle regeneration and considered the fibrosis to be compensatory to weakening of the wall, according to the old Thoma theory. MacLean (1929) and Klotz and Lloyd (1930) have given clear evidence of the influence of infectious disease in the production of degeneration, inflammation and fibrosis of the coronary arteries. It has been suggested that the medial disease may lead to aneurysm formation or rupture, and Gastewa (1933) has reported a case of cerebral hemorrhage believed to be due to the vascular lesion of typhoid fever.

It may be said that general infectious diseases are capable of producing degenerative, exudative and proliferative lesions of the arterial system.

The reports of Mandelstamm (1932) and Gouley, Bellet and McMillan (1933) on tuberculous arteritis, Seifried and Cain (1932) on arterial lesions of hog cholera, Hansmann and Schenken (1932) on melitensis meningo-encephalitis, Schenken and Hansmann (1932) on intestinal arteries in mercuric chloride poisoning, of Lillie (1932) on Rocky Mountain spotted fever, and Gerstel (1933) on pneumoconiosis, indicate that no sharp line can be drawn between degenerative and inflammatory lesions. This is emphasized in the study of polyarteritis nodosa by Klinger (1931), who in an examination of 2 cases found in one pronounced exudation and in the other degeneration and fibrosis, but with an overlapping of the different types of lesion in both cases.

One feature of the degeneration, namely, edema of the media with separation of muscle cells and granular precipitate, has been questioned. Scharpf (1909) thought it to be not pathological. Segre and Kellner (1921-22) found it to be common in various types of disease and demonstrated that it is not postmortem artefact. They hypothesized that agonal contraction of the artery presses plasma into the walls, but they do not defend the mechanical objections nor explain why the supposed plasma is usually basophilic. Schultz (1927), however, accepted their view. Our studies usually indicate that edema is related to, or identical with, the chromatropic substance of arteriosclerosis and of idiopathic medial necrosis (Moritz, 1933).

The intimal thickening is usually cellular but may be acellular, and its nature as it affects the smaller arteries is difficult to determine. In spite of reports that it is fatty, technical limitations render this difficult to determine. It is only in extremely small part chromatropic. Krompecher (1930) believed it to be an elastica "hypertrophy," but it does not regularly stain specifically. Whether the cells which participate in the thickening are endothelial, subendothelial fibroblasts, medial fibroblasts growing through ruptured elastica, or are the hypothetical elastoblasts of Krompecher has not been determined. That the presence of elastoblasts must be assumed to explain apparent hyperplasia of elastica is not borne out by the studies of Bloom (1929), who found elastica proliferation in tissue culture without cell participation. This would indicate that at least some of the fraying of elastica is proliferative. The studies of McMeans (1915) show that fraying can be degenerative, resulting from solution of the outer sheath of the fibers. As contrasted with fraying, swelling and fragmentation must certainly be degenerative. Provided the possibility be kept in mind, we disagree with Stoerk and Epstein (1920) that fragmentation is difficult to distinguish from normal fenestration.

VASCULAR LESIONS IN RHEUMATIC FEVER

That rheumatic fever may produce arterial lesions like those of other infectious disease is well known. De Mussy (1872) and Martin (1883)

made this suggestion, as did Legroux (1884), Hannot (1894) and Astier (1897).

Rabé (1902) described a proliferative endarteritis in association with medial edema. Takayasu (1909) interpreted this endarteritis hyperplastica as the result of organization and canalization of emboli, but Geipel (1909) regarded it as an irritative intimal proliferation in response to emboli. In our opinion, neither of these explanations is satisfactory because the evidence is plainly against its origin from either thrombosis or embolism. Gräff (1929) explained the fibrosis as being due to proliferative thickening of pre-existent capillaries, but this cannot well be harmonized with the mature development of arterial structure actually observed. Geipel (1909) described endothelial and collagenous hyperplasia in the intima, fibrin deposit in the subintimal connective tissue, marked narrowing of the lumen, and destruction of elastica interna. Intimal fibrosis was also noted by Klotz (1912), Coombs (1924), Sacks (1925-26) and others. Subsequent to their reports on aortic lesions (1923-24) Pappenheimer and Von Glahn (1927) described lesions in aortic vasa vasorum like those described in peripheral arteries by Von Glahn and Pappenheimer (1926). These findings were much like those of Geipel, but with some differences and given in greater detail. The intimal lesions observed were swelling and basophilia of the endothelium, the endothelial layer often elevated by coagulated exudate between it and the elastica. They described swelling, beading, and destruction of elastica interna. In addition they noted infiltration of a few wandering cells and polymorphonuclears into a loose intimal tissue in a coronary artery. Kugel and Epstein (1928) described intimal proliferation and increased lamellation of elastica in the vasa vasorum of the pulmonary artery, not considered to be specifically rheumatic and perhaps common to infectious diseases. Similar lesions have been described in the small divisions of the pulmonary artery by Paul (1928), Eiman and Gouley (1928), and McClenahan and Paul (1929). Gray and Aitken (1929) found widespread thickening of small arteries, principally by intimal fibrosis, sometimes eccentric and usually hyalinized.

MacCallum (1925) described multiple thrombosis which he attributed to primary vascular disease, a view evidently shared by Sacks (1925-26), v. Santha (1932) and others, including ourselves. The supposition of Takayasu (1909) and Geipel (1909) that emboli are sufficiently frequent to cause the widespread intimal lesions observed is not consistent with the actual occurrence of embolism in rheumatic fever.

Medial lesions vary from edema to necrosis and ultimately fibrosis. Rabé (1902) described a vacuolated state of the media, an "état réticulaire," which he attributed to degeneration and liquefaction. This occurs in numerous other conditions, as was recognized by Rabé, and is probably edema rather than liquefaction. Actual necrosis has been ob-

served and was described by Sacks (1925-26) in renal arteries. Von Glahn and Pappenheimer (1926) described extravasation of blood, which they attributed to the vascular necrosis. Edema and chromotropic change and fibrosis have been discussed above as related to infectious disease in general, and there is no reason for assuming that they operate differently in rheumatic fever. The special relation of fibrinoid degeneration to rheumatic fever has been emphasized by Klinge (1930, 1931) but, as indicated in the discussion of hyperergy below, this may occur in other conditions. He found that it originated in the intima and extended into the media, but in our experience it is far more common in media than in intima. Infiltration of lymphocytes and large mononuclears and sometimes polymorphonuclears has been described by many writers, but is generally regarded as an extension from similar infiltrations in the adventitia.

Cell infiltration in the adventitia was well described by Von Glahn and Pappenheimer (1926), who found that an infiltration of irregularly shaped mononuclear and polymorphonuclear cells may be followed by infiltration of lymphocytes and plasma cells. Klotz (1912) assumed that the cells originally in the adventitia infiltrate into the media by way of lymphocytes. This seems to be especially true in large arteries with vasa vasorum, which in the media may be encircled by the infiltrate. MacCallum (1925) found large cells in the adventitia, but appears to have associated these with intravascular thrombi. Aschoff (1906) noted the extension of submiliary nodules into the coronaries, a feature further described by Coombs (1907, 1908-09, 1911). Generally this involvement is confined to the adventitia, but it may extend into the media. Wätjen (1921) has described actual destruction of elastica in the course of this penetration. Swift (1924), MacCallum (1925), and others have referred to compression of coronaries by the submiliary nodules, a matter discussed subsequently in this paper. Many observers have reported on fibrosis in the adventitia.

Of the larger vessels, the pulmonary artery has been studied by Paul (1928), Eiman and Gouley (1928), Kugel and Epstein (1928), McClenahan and Paul (1929), Chiari (1930, 1931), and others. The lesions in the vasa vasorum are like those of other small arteries in rheumatic fever. There is perivascular infiltration of large mononuclears, often irregular in outline, and a relatively smaller number of lymphocytes. This sleeve of cells accompanies some of the vasa into the media, where it is accompanied by destruction of elastica and muscle. Splaying and fragmentation of the elastica interna are accompanied by variable degrees of intimal fibrosis.

Klotz (1912) described the aortic lesions of rheumatic fever as penetration into the media of vasa vasorum, edema, interruption of medial elastica and muscle, perivascular infiltration of plasma cells and lympho-

cytes, together with diffuse and perivascular infiltration of plasma cells and lymphocytes into the adventitia. Pappenheimer and Von Glahn (1923-24, 1926) believed that they could identify cells in adventitia and also in media as typical Aschoff cells and described Aschoff nodules in the adventitia. They were of the opinion that the aorta may be affected primarily by way of the intima as well as through the vasa vasorum. Giraldi (1929) confirmed Klotz' observations and noted intimal proliferation in the vasa vasorum. Chiari (1928), Laubry and associates (1930) and others have reported similar findings. Barnard (1929) described ringlike fibrosis of the aortic adventitia, but did not establish his case as definitely rheumatic. Schulz and Klinge (1933) have set up criteria for the diagnosis of chronic aortitis of rheumatic origin.

That medial destruction may be of especial import is indicated in the report by Gray and Aitken (1929) of a dissecting aneurysm of the aorta, presumably of rheumatic origin. Lisi's (1930) hepatic artery aneurysm was probably mycotic rather than the result of rheumatic arterial disease. Dawson (1933) found definite vascular lesions in the subcutaneous nodules of both rheumatic fever and rheumatoid arthritis. Coburn (1933) attributed multiple small hemorrhages to rheumatic vascular disease. Cracuin and associates (1933) in their review accept the existence of rheumatic disease of smaller arteries and coronaries.

Relation to Hyperergy.—The general character of rheumatic fever as a hyperergic reaction has been considered by Swift, Derick and Hitchcock (1928). The extensive studies of Klinge have supported this hypothesis. The pathogenesis of the lesion in vessel walls, as in other structures, was summarized by Klinge and Vaubel (1931) as (1) swelling of the connective tissue ground substance with variable degrees of fibrinoid change, (2) growth or hyperplasia of the connective tissue cells with or without basophilia of the cytoplasm, accompanied by variable degrees of lymphocyte leucocyte inflammation, (3) hyaline scar formation with or without elastica destruction. The connective tissue injury was not thought to be absolutely specific for rheumatic fever. They pointed out, however, that the fibrinoid change is found otherwise only in periarteritis nodosa, malignant sclerosis, certain forms of cardiovascular sepsis, Buerger's disease and focal glomerulonephritis. These may all be hyperergic manifestations. Although they claimed that experimentally multiple injections of streptococci are required for the production of fibrinoid, Apitz (1933) found it following repeated injections of serum; Henschen (1927) described it in areas of prolonged passive hyperemia; and Therese (1893) is quoted as having produced it by single injections of bacteria.

Fahr (1930) expressed the view that Klinge had not sufficiently demonstrated the similarity of experimental hyperergy and rheumatic fever,

but Metz (1931) was in complete agreement with Klinge as was Apitz (1933) and in essence also Klotz and Lloyd (1930), and Semsroth and Koch (1930).

CORONARY ARTERIES IN RHEUMATIC FEVER

The fact that coronary arteries are involved is indicated by studies quoted above. The frequency of the coronary lesions has been the subject of differences of opinion. Klotz (1912) stated that the finer ramifications of the coronaries are invariably affected, a view shared by Coombs (1924), but MacCallum (1925) regarded coronary disease as uncommon save in severe cases. Only a few studies have been directed to this phase of the problem.

Perry (1929-30) examined in detail the large coronaries of nine patients, from five to nineteen years of age, one of whom had had angina. Involvement was noted in all. The intima showed patchy or diffuse thickening by a loose tissue, which often was acellular or showed lymphocyte infiltration near the media. The elastica interna varied greatly—from practically normal to marked splaying sometimes so bulky as to suggest proliferation. Intimal fibrosis was variable. In the media he observed loss of nuclei, the "état reticulaire" of Rabé, infiltration of lymphocytes often in a hyaline matrix. Fibrosis occurred principally in the inner half of the media in communication with intimal fibrosis. The adventitia showed fibrosis and lymphocyte infiltration of variable intensity. Fatty change was not present.

Klinge (1930) in describing the early collagenous swelling of the connective tissues in rheumatic fever referred to the same change in coronary arteries, together with the production of fibrinoid in the intima with extension into the media, sometimes accompanied by a leucocyte lymphocyte reaction, and with narrowing of the lumen. Those changes led to dissociation of the fibrous and muscle cells. He later (1931) described the subsequent states of infiltration of cells like those of the submiliary nodule, most often in the adventitia but involving in some instances the other coats. He suggested that some of the intima lesions might represent organization of thrombi. The whole process led to fibrosis. He found elastica changes in those instances of granuloma formation within the arterial wall.

Relation to Other Similar Vascular Diseases.—It is difficult to orient the vascular lesions of rheumatic fever in the whole group of arterial diseases. Aschoff (1906), Ophüls (1923), and others have suggested a relation between the lesions of rheumatic fever and polyarteritis nodosa. Fahr (1920) suggested that rheumatic arterial disease may play a part in the etiology of malignant sclerosis and (1921) drew attention to the resemblance between the arterial lesions of rheumatic fever, polyarteritis nodosa and dermatomyositis (polymyositis). Gruber (1923, 1925) be-

lieved polyarteritis nodosa to be a manifestation of hyperergic reaction. Klinge and Vaubel (1931) appear to have considered that periarteritis nodosa, malignant sclerosis, certain forms of cardiovascular sepsis, thromboangiitis obliterans, focal glomerulonephritis and rheumatic fever are grouped together on the basis of hyperergic etiology. Semsroth and Koch (1930) as well as Metz (1931) expressed the view that the arterial lesions of acute infectious diseases, rheumatic fever, and polyarteritis nodosa are manifestations of the allergic state which differ only in degree of involvement. Klinger (1931), an adherent of the Ricker school, did not share in this assumption. Jäger (1932) placed the juvenile form of thromboangiitis obliterans in this general category.

v. Santha (1932) and others considered the vascular lesions of chorea as identical with those of rheumatic fever, which is true of our experience. We agree with his view that thrombi are secondary to lesions of the vessels rather than that they are emboli from heart valves.

Relation to Arteriosclerosis.—The significance of infectious disease in the origin of arteriosclerosis is debatable, and MacCallum (1933) believed that there is insufficient evidence for such an assumption. Klotz (1914-15, 1915) adhered to the inflammatory origin of arteriosclerosis and with Lloyd (1930) expressed the view that infectious diseases including rheumatic fever are of importance for the inception of coronary sclerosis, a view shared by MacLean (1929), Siegmund (1929), Giralaldi (1929) and Laubry (1930). Wiesel (1923) specifically attributed juvenile sclerosis to rheumatic lesions of the media, but this view is not accepted by Zeek (1932), who, however, found that rheumatic heart disease predisposes to early development of atheromatous lesions of the coronary arteries. Schulz and Klinge (1933) have described a chronic fibrous rheumatic aortitis, which is in reality a form of arteriosclerosis.

Relation to Myocardial Disease.—The question as to whether or not the coronary arterial lesions are the cause of myocardial damage of rheumatic fever has been discussed extensively. Hayem (1869, 1870) suggested it, and Krehl (1890) and Romberg (1894) considered it to be of great importance. This was combated by Aschoff (1904) and Aschoff and Tawara (1906), who also doubted the relation of the myocarditis to cardiac weakness. Fahr (1921) and Swift (1924) were definitely of the opinion that interference with myocardial nutrition from rheumatic disease of the smaller coronaries can cause myocardial insufficiency, and Klotz (1926) was equally certain that the myocardial scars are largely the result of the vascular disease. Slater (1930) attributed the scars to both arterial disease and direct inflammatory destruction of muscle. Brown (1932) found little evidence to support the view that the scarring results from inflammatory destruction and concluded that coronary disease is the most important etiological factor. Of her 115 cases, 15 were associated with rheumatic fever.

Disturbance of Cardiac Rhythm, and Pain.—Although case reports had previously appeared, the paper by Parkinson, Gosse and Gunson (1919-20) directed attention to the fact that irregularity of the heart action is common in rheumatic fever, and they attributed delayed conduction to myocardial inflammation. Cohn and Swift (1924) confirmed and amplified this report. Swift (1924) stated that interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of the impulse-conducting fibers supplied by the involved blood vessels. Besançon and Weil (1926) described in detail auriculoventricular dissociation. Swift (1928) noted that arrhythmias are found in various types of infectious disease but are especially common in rheumatic fever, a view evidently shared by Lukomski (1932, 1933) and others. Slater's case is probably one of extensive infarction. Levy and Turner's (1929) report is representative of the modern view of the subject. They noted the frequency of disturbances of auriculoventricular conduction in rheumatic hearts and found that delay is more common than complete block. Although usually temporary, the disturbances may persist for a long time after subsidence of the acute rheumatic cycle. They expressed the view that in the absence of syphilis or of digitalis administration, the occurrence of prolonged P-R interval or of block in patients less than thirty-five years of age is presumptive evidence of rheumatic heart disease. They suggested that the occurrence of leucocytosis in the active stages indicates that the functional disorder may be attributed to myocardial damage, the result of occlusion of arterial twigs. Oettinger and Neslin (1932) found 14 cases of A-V dissociation in 200 cases of rheumatic carditis. This lasted usually only a few days. Their explanation was a hypothetical irritation of Tawara's node or of the automatic function of the sinus node.

Coronary occlusion is not a frequent complication of rheumatic fever. Wearn (1923) found a positive history in only one of his 19 cases, Levine and Brown (1929) in only three of 145 cases. Conner and Holt (1930) did not mention it in their large series. White and Jones (1928) mentioned it in one of 71 cases. Kerr, Larkey, and Larsen (1924) recorded definite rheumatic involvement in their four cases. Breitnecker (1931) has described a fatal case of thrombosis in the rheumatic heart of a girl twenty-two years old.

Cardiac pain and discomfort are well known in rheumatic fever. Gallivardin (1908) reported a case of severe pain in a seven-year-old child, and seems to have attributed the trouble to myocardial scars. Kahn (1926) laid great emphasis on infectious diseases and rheumatic fever and reported that of 82 cases of angina, 24 patients had a history of frequent tonsillitis and 20 of rheumatic fever. White and Mudd (1927) reported 8 cases of angina in patients from seventeen to twenty-six years of age, all of whom had rheumatic hearts and aortic insuf-

iciency. Stolkind (1928) reported one patient, thirteen years old, who had angina, rheumatic heart disease and aortic insufficiency. He also reported 12 cases from the literature in patients from seven to fourteen years of age, of whom only 2 are shown to have had aortic insufficiency. It is unfortunate that only a few of the cases reported by White and Mudd and by Stolkind came to autopsy. White and Jones (1928) found a history of rheumatic fever in 7 of their 77 cases of angina in adults. Swift and Hitchcock (1928) did not think the pain to be due to coronary or aortic disease in the ordinary sense, but rather to perivascular and adventitial lesions as foci of irritation.

It can be said that while proved coronary thrombosis is rare in rheumatic fever, this is not true of cardiac pain. If cardiac pain be analyzed as it occurs in all age groups, rheumatic fever appears to play a small part, except in such reports as that of Kahn. If, however, it be considered in young patients, rheumatic fever is a common association of the cardiac pain. Certainly many of these patients show aortic insufficiency, but this is not true of all, and even in those with aortic valve involvement the coronary twigs have not been regularly studied. Disease of these twigs is undoubtedly frequent, as we shall demonstrate in this paper, and it is also possible that adventitial and perivascular lesions may well cause interference with the blood supply to the myocardium. Thus it must be accepted that cardiac ischemia cannot be excluded as the cause of the cardiac pain of rheumatic heart disease.

MATERIAL AND METHOD

For this study, 56 hearts were selected from the recent autopsy material of Lakeside Hospital, Babies' and Children's Hospital and Cleveland City Hospital. Only hearts which showed Aschoff nodules or typical rheumatic inflammation were included. Several hearts, ordinarily acceptable as rheumatic, were excluded because Aschoff nodules were not found, even though they showed definite valvular disease. Otherwise the hearts were taken in order as they occurred in the regular autopsy series, and were in no way selected because they showed vascular lesions. Of the 56 patients, 48 gave a history of rheumatic fever, except one who had chorea. There were 15 patients in the first decade, 12 each in the second and third, 10 in the fourth, and 7 in subsequent decades. There were 26 males and 30 females, 44 whites and 12 colored. Forty nonrheumatic hearts were examined as controls, but in many of these infections were present somewhere in the body. The histological material was fixed in neutral formalin, embedded in paraffin, cut at 5 to 7 micra, and routinely stained with hematoxylin and eosin. Special stains included the Verhoeff elastica method, Mallory's connective tissue stain, van Gieson-hematoxylin, Masson trichrome with light green, scarlet R, and for chromotropic substance heavy staining with hematoxylin or

staining with thionin or polychrome methylene blue. The special methods were not used routinely but were employed frequently to clarify features indicated in the hematoxylin and eosin stains.

The observations were recorded on a chart for each heart, and Table I is a summary of the first decade, which illustrates the method for each heart.

RESULTS

First Decade.—The details are to be found in Tables I and II. The lesion observed in the pulmonary arteries was principally in the form of pitting of the intima above the pulmonic orifice. Post-mortem blood cultures were negative in 9 cases, in one yielded *B. coli* and an unidentified streptococcus, and in another streptococcus gamma.

TABLE I

DATA ON RHEUMATIC CORONARIES, FIRST DECADE

Evidence of Rheumatic Fever

Clinical 12; Aschoff nodules 15; rheumatic inflammation 12.

Valve lesions: acute only 2; chronic only 4; both 9.

Coronaries 2; pulmonaries 7; aorta 6.

No note coronaries 3; pulmonaries 2; aorta 2.

Main Coronaries (None in sections 2)

Adventitia: Aschoff 5; fibrosis 6; other cells 6.

Media: edema 13; chromotropic 4; cells 2; fibrosis 4.

Intima: edema 10; chromotropic 4; cells 1; fibrosis 11.

Elastica interna: splitting 9; fragmentation 10; swelling 10.

Other elastica: fragmentation 3; swelling 3.

Thrombosis —; *Fibrinoid*: intima 5; media 4.

Medium-Sized Coronaries

Adventitia: Aschoff 7; fibrosis 8; other cells 6.

Media: edema 15; chromotropic 5; cells 2; fibrosis 4; necrosis 4.

Intima: edema 7; chromotropic —; cells 1; fibrosis 3.

Elastica interna: splitting 3; fragmentation 6; swelling 5.

Other elastica: fragmentation 1; swelling 1.

Thrombosis —; *Fibrinoid*: intima 2; media 8; adventitia 1.

Small-Sized Coronaries

Adventitia: Aschoff 9; fibrosis 7; other cells 8.

Media: edema 13; chromotropic 3; cells 1; fibrosis 1; necrosis 4.

Intima: edema 7; chromotropic —; cells —; fibrosis 3.

Elastica interna: splitting 1; fragmentation 3; swelling 1.

Other elastica: fragmentation —; swelling —.

Thrombosis 2; *Fibrinoid*: intima 2; media 5; adventitia 3.

In summary, the coronary tree in parts showed edema in all cases, associated with fibrinoid in all, and with chromotropic change in 7 cases. Necrosis was observed in 6 cases. Inflammatory reaction as shown by lymphocytes, plasma cells, endothelial cells and sometimes polymorphonu-

clears was found in the adventitia in 9 cases and in other coats in 5 cases. The Aschoff nodules were found in the adventitia in 11 cases and in the media in one case. Elastica changes were observed in all but 2 cases, in both of which adventitial inflammation was observed, in one with medial necrosis and in the other associated with inflammation and thrombosis of veins. Fibrosis of the adventitia was observed in 10 cases, of the media in 5 cases, and of the intima in 12 cases. Degenerative changes were found in all cases and in all were associated with either inflammation or fibrosis, or both. In 3 cases the various types of lesion were not all present. In a colored female two and one-half years

TABLE II
FIRST DECADE—CORONARY LESIONS

	COLOR	SEX	AGE (YEARS)	EDEMA	CHROMOTROPIC	FIBRINOID	NECROSIS	ELASTICA ALTERATIONS	ASCHOFF NOD-ULES		IN-FLAM-MATIONS		FIBROSIS			GROSS SCLEROSIS	
									ADVENTITIA	MEDIA	ADVENTITIA	MEDIA	THROMBOSIS	.DVENTITIA	MEDIA		INTIMA
3985	B.	F.	2½	+	-	+	-	+	-	-	-	-	A	-	-	+	+
8690	B.	M.	4½	+	+	+	+	+	+	-	+	-	-	+	+	+	-
8687	B.	M.	5	+	+	+	+	+	+	-	+	-	-	+	+	+	-
3585	B.	F.	5	+	+	+	+	+	+	-	+	-	V	+	-	-	-
3999	W.	F.	6	+	-	+	-	+	+	+	+	-	V	-	-	-	-
4229	W.	F.	7	+	+	+	-	+	+	-	+	-	A	+	+	+	-
183	B.	M.	7	+	-	+	-	-	-	-	+	-	V	-	-	-	0
2	B.	M.	7	+	-	+	+	+	+	-	+	-	-	+	-	-	-
3782	W.	F.	7	+	+	+	+	+	-	-	+	-	-	+	-	+	0
377	W.	F.	7	+	+	+	-	+	-	-	-	-	-	+	-	+	+
3685	W.	M.	8	+	+	+	+	+	+	-	+	+	-	+	-	+	-
3923	W.	F.	8	+	-	+	-	+	-	-	-	-	-	-	-	+	-
3800	W.	F.	8	+	-	+	-	+	+	-	+	+	V	+	-	+	-
283	W.	F.	9	+	+	+	-	+	+	-	-	+	-	+	-	+	0
3819	W.	F.	10	+	+	+	-	+	+	-	+	+	V	+	+	+	-

In all tables: + means present. 0 means no note in protocol.
- means absent. V means vein.
A means artery.
C means capillary.

old, degeneration appeared to be the principal lesion, but it was accompanied by gross intimal fibrosis of the coronaries, more widespread microscopically, and definite swelling of the elastica. In a colored male seven years old the arterial lesion, in addition to degeneration, was only inflammation in the adventitia, but the veins showed edema, inflammation of adventitia and thrombosis. In another colored male seven years old the arterial degeneration was accompanied by actual medial necrosis and adventitial inflammation. If these cases be regarded as showing only slight arterial disease, 13 of the 15 cases showed significant disease in various parts of the coronary arterial tree.

TABLE III

DATA ON RHEUMATIC CORONARIES—SECOND DECADE

Evidence of Rheumatic Fever

Clinical 10; Aschoff nodules 12; rheumatic inflammation 10.
Valve lesions: Acute only 1; chronic only 1; both 9.
Coronaries 4; pulmonaries 2; aorta 7.
No note: coronaries 5; pulmonaries 3; aorta 1.

Main Coronaries (None in sections 2)

Adventitia: Aschoff -; fibrosis 3; other cells 5.
Media: edema 10; chromotropic 2; cells -; fibrosis 3; necrosis 1.
Intima: edema 10; chromatropic 1; cells 1; fibrosis 10.
Elastica interna: splitting 7; fragmentation 7; swelling 8.
Other elastica: fragmentation 3; swelling 1.
Thrombosis -; Fibrinoid: intima 5; media 8.

Medium-Sized Coronaries

Adventitia: Aschoff 4; fibrosis 6; other cells 5.
Media: edema 11; chromotropic 1; cells -; fibrosis 1; necrosis 4.
Intima: edema 7; chromotropic 1; cells -; fibrosis 7.
Elastica interna: splitting 2; fragmentation 4; swelling 5.
Other elastica: fragmentation -; swelling -.
Thrombosis -; Fibrinoid: intima 3; media 9.

Small-Sized Coronaries

Adventitia: Aschoff 9; fibrosis 4; other cells 4.
Media: edema 10; chromotropic -; cells 1; fibrosis 3; necrosis 4.
Intima: edema 3; chromotropic -; cells -; fibrosis 4.
Elastica interna: splitting 1; fragmentation 3; swelling 1.
Other elastica: fragmentation -; swelling -.
Thrombosis -; Fibrinoid: intima 3; media 9; adventitia 1.

TABLE IV

SECOND DECADE—CORONARY LESIONS

COLOR	SEX	AGE (YEARS)	EDEMA	CHROMOTROPIC	FIBRINOID	NECROSIS	ELASTICA ALTERATIONS	ASCHOFF NOD-ULES		IN-FLAM-MATIONS			FIBROSIS			GROSS SCLEROSIS	
								ADVENTITIA	MEDIA	ADVENTITIA	MEDIA	THROMBOSIS	ADVENTITIA	MEDIA	INTIMA		
4029	W.	M.	12	+	-	+	+	+	+	-	+	-	V	+	-	+	0
4106	B.	M.	12	+	-	+	+	+	+	+	-	-	-	+	-	+	0
3506	W.	F.	12½	+	+	+	+	+	+	-	+	-	V	-	-	+	+
344	B.	F.	13	+	+	+	-	+	+	+	+	-	-	+	+	+	+
427	W.	M.	13	+	-	+	-	+	+	-	-	-	-	+	-	+	0
412	W.	F.	13	+	-	+	-	-	+	-	-	-	C	-	-	-	-
3146	W.	F.	14	+	-	+	+	+	+	-	+	-	-	+	-	+	0
3709	W.	F.	14	+	-	+	-	+	+	-	+	-	V	-	-	+	-
3805	B.	M.	18	+	-	+	-	+	-	-	-	-	-	+	-	+	-
6653	W.	M.	19	+	+	+	+	+	+	+	+	+	V	+	+	+	+
3725	W.	F.	19	+	+	+	+	+	+	-	-	-	-	+	-	+	0
3809	W.	F.	20	+	-	+	-	+	-	-	+	-	A	+	-	+	+

Second Decade.—(See Tables III and IV.) One patient, a white male nineteen years old, died as the result of scarlatina, showed complete heart-block, had a typical rheumatic history and at autopsy typical rheumatic myocarditis without valve lesions, but the post-mortem blood culture showed streptococcus alpha. The main trunk of the pulmonary artery was atherosclerotic in 1 case, normal in 8 and not described in 3. The blood cultures showed no growth in 7 cases, streptococcus alpha in 1, streptococcus beta in 1, streptococcus gamma in 2 and *B. coli* and staphylococcus in 1.

In summary, the coronary tree in parts showed edema in all cases, associated with fibrinoid in all, and with chromotropic change in 3 cases. Necrosis was observed in 5 cases. Inflammatory reaction, as shown by cellular infiltration, was found in the adventitia in 5 cases and in other coats in only 1 case. Aschoff nodules were found in the adventitia in 9 cases but not in other coats. Elastica changes were observed in all but 2 cases, in one of which there was adventitial fibrosis with the presence of Aschoff nodules and in the other adventitial Aschoff nodules. Fibrosis was observed in the adventitia in 6 cases, in the media in 4 cases and in the intima in 11 cases. Degenerative changes were found in all cases and in all were associated with inflammation or fibrosis or both. In one case the additional change was only in the form of Aschoff nodules in the adventitia, but there were no sections of larger arteries, and in another case there were only the additional appearances of Aschoff nodules in the adventitia and intimal fibrosis. If these 2 cases be regarded as showing relatively insignificant arterial disease, 10 of the 12 cases showed significant disease in various parts of the coronary arterial tree.

Third Decade.—(See Tables V and VI.) The pulmonary arteries showed sclerosis in 3 cases, were not noted in 4 cases and revealed no change in 5 cases. Post-mortem blood cultures were negative in 4 cases, were not made in 3 cases; in 1 case yielded *Staphylococcus aureus*, in

TABLE V

DATA ON RHEUMATIC CORONARIES—THIRD DECADE

Evidence of Rheumatic Fever

Clinical 11; Aschoff nodules 12; rheumatic inflammation 11.

Valve lesions: acute only 1; chronic only 1; both 10.

Coronaries 3; pulmonaries 3; aorta 8.

No note 3; pulmonaries 4; aorta 1.

Main Coronaries (None in sections 2)

Adventitia: Aschoff 1; fibrosis 2; other cells 8.

Media: edema 9; chromotropic 5; cells —; fibrosis 2.

Intima: edema 8; chromotropic —; cells 1; fibrosis 8.

Elastica interna: splitting 8; fragmentation 9; swelling 8.

Other elastica: fragmentation 2; swelling 1.

Thrombosis 1; *Fibrinoid:* intima 8; media 8.

TABLE V—CONT'D

Medium-Sized Coronaries

Adventitia: Aschoff 3; fibrosis 11; other cells 6.
Media: edema 12; chromotropic 4; cells —; fibrosis 2; necrosis 5.
Intima: edema 5; chromotropic —; cells —; fibrosis 10.
Elastica interna: splitting 4; fragmentation 5; swelling 8.
Other elastica: fragmentation 1; swelling —.
Thrombosis 1; Fibrinoid: intima 6; media 8; adventitia 1.

Small-Sized Coronaries

Adventitia: Aschoff 6; fibrosis 11; other cells 7.
Media: edema 12; chromotropic 1; cells —; fibrosis 1; necrosis 7.
Intima: edema 5; chromotropic —; cells —; fibrosis 11.
Elastica interna: splitting 4; fragmentation 2; swelling 8.
Other elastica: fragmentation —; swelling 1.
Thrombosis 2; Fibrinoid: intima 7; media 10; adventitia 1.

TABLE VI
THIRD DECADE—CORONARY LESIONS

COLOR	SEX	AGE (YEARS)	EDEMA	CHROMOTROPIC	FIBRINOID	NECROSIS	ELASTICA ALTERATIONS	ASCHOFF NOD-ULES			IN-FLAM-MATIONS			FIBROSIS			GROSS SCLEROSIS
								ADVENTITIA	MEDIA		ADVENTITIA	MEDIA	THROMBOSIS	ADVENTITIA	MEDIA	INTIMA	
3398	W.	F.	21	++	—	+	—	+	—		+	—	A	+	—	+	—
3224	W.	M.	22	++	+	+	—	+	+	—	+	—	—	+	—	+	—
4050	W.	M.	22	++	+	+	+	+	—	—	+	Int- ima	A	+	—	+	+
6022	W.	M.	23	+	+	+	+	+	+	—	+	—	—	+	+	+	+
3864	B.	M.	24	+	—	+	—	+	+	—	+	—	V	+	—	+	0
3321	W.	M.	25	+	+	+	+	+	+	—	+	—	—	+	+	+	—
2307	W.	M.	26	+	—	+	+	+	+	—	—	—	V	+	—	+	—
3666	W.	M.	26	+	—	+	+	+	—	—	+	—	—	—	—	+	—
3773	W.	M.	26	+	+	+	+	+	—	—	+	—	AV	+	+	+	+
3235	W.	M.	29	+	—	+	+	+	+	—	+	—	—	+	—	+	0
4069	B.	F.	29	+	+	+	+	+	—	—	+	—	V	+	—	+	—
3355	W.	M.	30	+	+	+	+	+	+	—	+	—	—	+	+	+	0

another Gram-positive diplococci, in another streptococcus alpha, another streptococcus beta and another streptococcus gamma.

In summary, edema of some part of the arterial tree was found in all cases, with chromotropic substance in 7. Fibrinoid was observed in all cases and necrosis in 9. All cases showed elastica alterations. Aschoff nodules were found in the adventitia in 8 cases. Inflammation was observed in the adventitia in 11 cases and the intima in 1. Thrombosis in arteries was observed in 3 cases and in veins in 4 cases. Fibrosis was observed in the adventitia in 11 cases, in the media in 4 cases, and in the intima in all cases. In no case was the disease limited to degenera-

TABLE VII

DATA ON RHEUMATIC CORONARIES—FOURTH DECADE

Evidence of Rheumatic Fever

Clinical 10; Aschoff nodules 9; rheumatic inflammation 7.
Valve lesions: acute —; chronic only 4; both 6.
Coronaries 4; pulmonaries 6; aorta 10.
No note: coronaries 4; pulmonaries 2; aorta —.

Main Coronaries (None in sections 2)

Adventitia: Aschoff 1; fibrosis 5; other cells 7.
Media: edema 8; chromotropic 5; cells 2; fibrosis 7; necrosis 1.
Intima: edema 8; chromotropic 2; cells 1; fibrosis 8.
Elastica interna: splitting 8; fragmentation 8; swelling 8.
Other elastica: fragmentation 3; swelling 2.
Thrombosis —; Fibrinoid: intima 6; media 6.

Medium-Sized Coronaries

Adventitia: Aschoff 3; fibrosis 10; other cells 7.
Media: edema 10; chromotropic 3; cells —; fibrosis 2; necrosis 9.
Intima: edema 4; chromotropic —; cells —; fibrosis 5.
Elastica interna: splitting 4; fragmentation 7; swelling 9.
Other elastica: fragmentation —; swelling —.
Thrombosis —; Fibrinoid: intima —; media 8; adventitia 1.

Small-Sized Coronaries

Adventitia: Aschoff 5; fibrosis 10; other cells 6.
Media: edema 9; chromotropic —; cells —; fibrosis 3; necrosis 8.
Intima: edema 5; chromotropic —; cells —; fibrosis 6.
Elastica interna: splitting 1; fragmentation 6; swelling 6.
Other elastica: fragmentation —; swelling —.
Thrombosis —; Fibrinoid: intima 1; media 5.

TABLE VIII

FOURTH DECADE—CORONARY LESIONS

COLOR	SEX	AGE (YEARS)	EDEMA	CHROMOTROPIC	FIBRINOID	NECROSIS	ELASTICA ALTERATIONS	ASCHOFF IN-FLAM-MATIONS					FIBROSIS			GROSS SCLEROSIS
								ADVENTITIA	MEDIA	ADVENTITIA	MEDIA	THROMBOSIS	ADVENTITIA	MEDIA	INTIMA	
4042	W.	M.	32	+	—	+	+	+	—	+	—	V	+	+	+	0
3868	W.	F.	35	+	—	+	+	+	+	—	+	—	+	+	+	+
8727	W.	M.	37	+	+	+	+	+	—	—	+	—	+	+	+	+
3735	W.	F.	38	+	+	+	+	+	+	—	+	—	+	+	+	—
3053	W.	F.	39	+	—	+	+	+	+	+	+	—	+	+	+	0
4018	W.	F.	39	+	+	+	+	+	—	—	+	—	+	—	+	+
3418	W.	F.	39	+	+	+	+	+	—	—	+	—	+	—	+	0
3463	B.	F.	39	+	—	+	+	+	+	—	+	—	+	—	+	—
4016	W.	M.	39	+	+	+	+	+	—	—	+	—	+	+	+	+
3884	W.	M.	40	+	+	+	+	+	—	—	—	—	+	+	+	0

tion, and in this decade it can be stated that some part of the coronary arterial tree showed significant lesions in all cases.

Fourth Decade.—(See Tables VII and VIII.) The pulmonary arteries showed sclerosis in 6 cases, were negative in 2 and were not noted in 2. Post-mortem blood cultures were negative in 6 cases, not made in 3 cases and in 1 case yielded pneumococcus type IV.

In summary, edema of some sort of the arterial tree was found in all cases, combined with chromotropic substance in 6. Fibrinoid, necrosis, and elastica alterations were found in all cases. Aschoff nodules were present in the adventitia in 5 cases, invading the media in 1. Inflammation was found in the adventitia of 9 cases, invading the media in 1, the same case in which Aschoff nodule involvement was observed. Thrombosis was found in the veins of one case. Fibrosis of the adventitia was present in all cases, of the media in 7 cases and of the intima in all cases. One case only, a white male forty years old, failed to show inflammatory lesions of the arteries, but the vessels showed all the forms of degenerative lesion as well as fibrosis of all three coats.

Fifth and Subsequent Decades.—(See Tables IX and X.) The pulmonary arteries were sclerotic in 5 cases and negative in 2. Post-mortem blood cultures were negative in 5 cases and were contaminated in 2.

TABLE IX

DATA ON RHEUMATIC CORONARIES—FIFTH AND SUBSEQUENT DECADES

Evidence of Rheumatic Fever

Clinical 5; Aschoff nodules 7; rheumatic inflammation 7.

Valve lesions: acute —; chronic only 2; both 5.

Coronaries 6; pulmonaries 5; aorta 6.

No note: coronaries 1.

Main Coronaries (None in sections 2)

Adventitia: Aschoff —; fibrosis 3; other cells 4.

Media: edema 5; chromotropic 3; cells —; fibrosis 4; necrosis 1.

Intima: edema 5; chromotropic —; cells —; fibrosis 5.

Elastica interna: splitting 4; fragmentation 5; swelling 5.

Other elastica: fragmentation —; swelling —.

Thrombosis —; *Fibrinoid:* intima 3; media 4.

Medium-Sized Coronaries

Adventitia: Aschoff 3; fibrosis 5; other cells 5.

Media: edema 7; chromotropic 2; cells —; fibrosis 3; necrosis 3.

Intima: edema 2; chromotropic 1; cells —; fibrosis 5.

Elastica interna: splitting 2; fragmentation 6; swelling 7.

Other elastica: fragmentation —; swelling —.

Thrombosis 1; *Fibrinoid:* intima 2; media 6.

Small-Sized Coronaries

Adventitia: Aschoff 5; fibrosis 7; other cells 5.

Media: edema 7; chromotropic 2; cells —; fibrosis —; necrosis 6.

Intima: edema 2; chromotropic —; cells —; fibrosis 7.

Elastica interna: splitting 1; fragmentation 4; swelling 5.

Other elastica: fragmentation —; swelling —.

Thrombosis —; *Fibrinoid:* intima 3; media 4; adventitia 2.

TABLE X
FIFTH AND SUBSEQUENT DECADES—CORONARY LESIONS

	COLOR	SEX	AGE (YEARS)	EDEMA	CHROMOTROPIC	FIBRINOID	NECROSIS	ELASTICA ALTERATIONS	ASCHOFF NOD-ULES		IN-FLAM-MATIONS		FIBROSIS			GROSS SCLEROSIS	
									ADVENTITIA	MEDIA	ADVENTITIA	MEDIA	THROMBOSIS	ADVENTITIA	MEDIA		INTIMA
3859	W.	F.	43	+	+	+	+	+	-	-	+	-	-	+	+	+	+
3933	W.	F.	43	+	+	+	+	+	+	-	+	-	-	+	+	+	0
3606	W.	M.	44	+	-	+	+	+	+	-	+	-	-	+	+	+	+
3883	W.	F.	50	+	-	+	+	+	+	-	+	-	-	+	+	+	+
3356	W.	M.	58	+	+	+	+	+	+	-	+	-	-	+	+	+	+
3820	W.	F.	63	+	-	+	+	+	+	-	+	-	A	+	-	+	+
3744	W.	F.	67	+	+	+	+	+	+	-	+	-	-	+	-	+	+

In summary, edema of some part of the arterial tree was present in all cases, with chromotropic substance in 4. Fibrinoid, necrosis, and elastica alterations were found in all cases. Aschoff nodules were found in the adventitia in 6 cases, without invasion of media. Adventitial mononuclear cell infiltration was found in all cases. Arterial thrombosis was found in 1 case. Fibrosis was observed in adventitia and intima of all cases and in the media of 5. All cases showed degenerative and inflammatory lesions and fibrosis.

SUMMARY OF RESULTS

All cases showed edema of some part of the arterial tree. Chromotropic change was found to be about equally frequent in all decades except the second, in which one-third of the cases showed it as compared with about two-thirds in the other decades. Fibrinoid was found in all cases. Necrosis increased in frequency as age advanced. It was observed in 40 per cent of the cases of the first decade, 50 per cent of the second, 75 per cent of the third, and 100 per cent subsequently. Elastica alterations were found in about 90 per cent of the cases in the first 2 decades and in all cases thereafter. Aschoff nodules in the adventitia were somewhat more frequent in the first three decades than in subsequent decades. Their invasion into the media was

PLATE I

- Fig. 1.—Edema of media, the so-called “état reticulaire,” in a small epicardial coronary artery. Female, aged two and one half years. Hematoxylin and eosin Wratten green filter B-58. $\times 150$.
- Fig. 2.—Edema of intima and media in large epicardial vein. Female, aged twenty years. Hematoxylin and eosin. Wratten green filter B-58. $\times 215$.
- Fig. 3.—Necrosis in media of small intramural artery, with a small vacuolated area of edema. Male, aged five years. Hematoxylin and eosin. Wratten green filter B-58. $\times 335$.
- Fig. 4.—Fibrinoid degeneration in upper media of large coronary artery, with many nodal points. Female, aged thirty-five years. Hematoxylin and eosin. Wratten green filter B-58. $\times 230$.

FIG. 2.

FIG. 4.



FIG. 1.

FIG. 3.

Fig. 6.

Fig. 8.



Fig. 5.

Fig. 7.

more frequent in the first 2 decades than later. Infiltration of mononuclear cells into the adventitia was observed in about two-thirds of the cases of the first 2 decades, about 90 per cent of those of the third and fourth decades, and in all the older cases. Infiltration into the media was present in 27 per cent of the cases of the first decade, 8 per cent of those of the second, 20 per cent of those of the fourth, and in none of those of the third, fifth and subsequent decades. Thrombosis was noted in the smaller arterics in 6 cases, in the capillaries in one case and in the veins in 14 cases, a total of 21 cases or 37 per cent of the series. It was found in about one-half of the cases of the first three decades and in about 10 per cent of those of subsequent decades. Fibrosis of the adventitia was observed in 73 per cent of the cases of the first decade, 58 per cent of those of the second, 92 per cent of those of the third, and all of the cases in later periods. Fibrosis of the media was found in 26 per cent of the cases of the first decade, 17 per cent of those of the second decade, 33 per cent of those of the third, and 70 per cent of those of the fourth and subsequent decades. Fibrosis of the intima was noted in 73 per cent of the cases of the first decade, 92 per cent of those of the second, and all the cases of the third and subsequent decades. Of the cases in which notation was made, grossly observable sclerosis of the coronaries was found in 18 per cent in the first decade, 56 per cent in the second, 33 per cent in the third, 66 per cent in the fourth, and all in the fifth and subsequent decades. Microscopically, severe fibrosis of the intima of the large divisions of the coronaries (when present in the sections) was observed in 38 per cent of the cases of the first decade, 50 per cent of those of the second, 70 per cent of those of the fourth, and all the cases of the subsequent decades. Of 28 patients between the ages of nineteen and forty-four years inclusive, 5 showed sclerosis almost completely occlusive, all males, aged 19, 23, 29, 40 and 44 years respectively.

Thus it is apparent that age has no influence upon edema, chromotropic change, fibrinoid or incidence of Aschoff nodules in the adventitia. As age advances there is an increased incidence of necrosis, elastica alterations, infiltration of mononuclear cells in adventitia, fibrosis of each coat of the arteries and grossly observable sclerosis. The incidence of thrombosis is markedly decreased after the third decade.

Degenerative lesions were found commonly in the controls and are not regarded as significant. In the 56 rheumatic hearts they were ac-

PLATE II

Fig. 5.—Swelling, fragmentation and fraying of elastica in large coronary artery. Female, aged eighteen years. Verhoeff elastica. Wratten orange filter G-15. $\times 165$.

Fig. 6.—Marked swelling and fragmentation of elastica in large coronary artery. Female, aged thirty-two years. Verhoeff elastica. Wratten orange filter G-15. $\times 165$.

Fig. 7.—Marked swelling and wrinkling of elastica in small intramural coronary artery, with apparent reduction of lumen. Male, aged twenty-nine years. Hematoxylin and eosin. Wratten green filter B-58. $\times 230$.

Fig. 8.—Aschoff nodules involving adventitia in a small intramural coronary artery. Male, aged seven years. Hematoxylin and eosin. Wratten green filter B-58. $\times 140$.

accompanied by acute inflammatory lesions alone in 3 instances, by fibrotic lesions alone in 4 instances, and by both in 49 instances. If both degenerative and inflammatory lesions be excluded, 52 of the 56 hearts showed significant lesions of some part of the coronary tree. The coronaries of two cases, a seven-year-old colored boy and a thirteen-year-old white girl, failed to show elastica alterations, but both these showed inflammatory lesions. Three cases, a seven-year-old white girl, an eight-year-old white girl and a forty-year-old white woman, failed to show inflammatory lesions of the arteries, but all showed intimal fibrosis.

All cases showed intimal fibrosis except 4 in the first decade (all of which exhibited inflammation, and of these 2 showed also venous thrombosis) and one in the second decade which showed Aschoff nodule involvement of adventitia and capillary thrombosis.

Blood cultures showed no apparently significant relation between bacteremia and thrombosis. Of 10 cases from which streptococci were recovered, 5, or 50 per cent, showed thrombosis. Of 31 cases in which the blood culture showed no growth, 11, or 35 per cent, showed thrombosis. Of 12 cases from which organisms other than streptococci were isolated, none showed thrombosis.

DISCUSSION OF RESULTS

In order that the findings might be subjected to further control than that of an extensive experience, the sections from 40 nonrheumatic hearts were examined. These were from patients who had died of infectious disease of short duration, from tumors, poisoning, etc. Definitely cardiovascular cases were excluded. Naturally the tumor patients and those dead of other prolonged disease showed terminal infections. The patients varied in age from eleven months to fifty-eight years. Edema and necrosis of some part of the coronary tree were observed in all cases. Chromotropic substance was not observed. Fibrinoid was found in 18 of the 40 specimens. In the first two decades, comprising 11 cases, elastica change was limited to slight swelling, and the youngest patient to show fragmentation or splitting was twenty-four years old. After that age the more severe elastica lesions were found in 18 of 31 hearts. Fibrosis of the intima was found in only one of the 11 patients

PLATE III

Fig. 9.—Exudative inflammation of medium-sized intramural coronary artery. Female, aged nine years. Adventitia shows fibrosis and polymorphonuclear leucocytes. Media shows fibrosis, edema, infiltration of polymorphonuclears and mononuclears. The intima is destroyed and shows cellular infiltration and marked fibrin formation. There is no organization of the marginal fibrin and the lumen contains erythrocytes. The process reduplicates the endocardial lesion of the same heart. Clinically chorea. Hematoxylin and eosin. Wratten green filter B-58. $\times 82$.

Fig. 10.—Mural fibrin thrombus attached to markedly thickened intima of large coronary artery. Male, aged twenty-four years. Hematoxylin and eosin. Wratten green filter B-58. $\times 150$.

Fig. 11.—Communicating fibrosis of intima and media with distortion of architecture (metallaxis) in large coronary. Female, aged thirteen years. Hematoxylin and eosin. Wratten green filter B-58. $\times 125$.

Fig. 12.—Marked fibrosis of intima with disorganization of media in large coronary. Female, aged ten years. Hematoxylin and eosin. Wratten green filter B-58. $\times 125$.

FIG. 10.

FIG. 12.

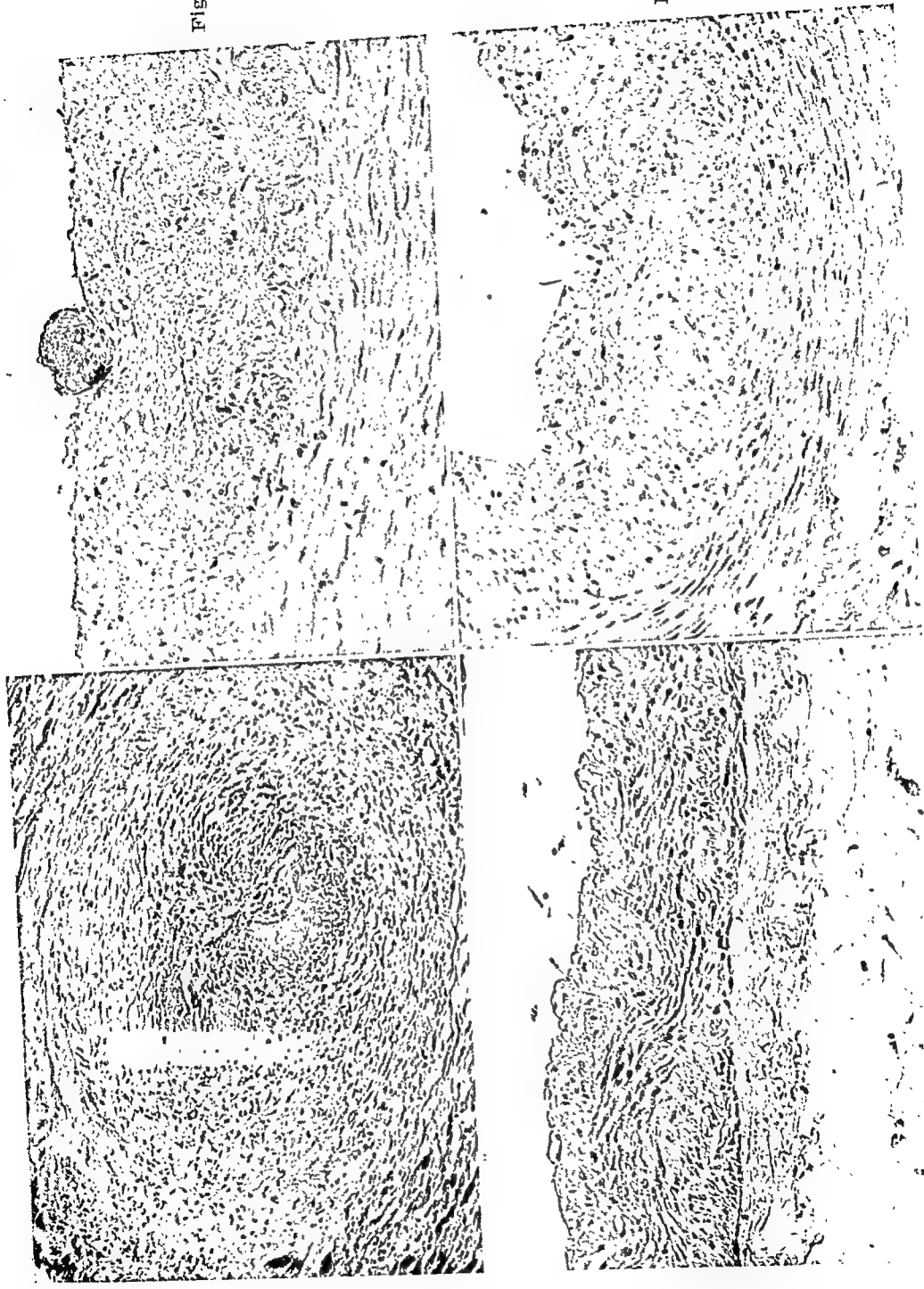


FIG. 9.

FIG. 11.

Fig. 14.



Fig. 16.



Fig. 13.

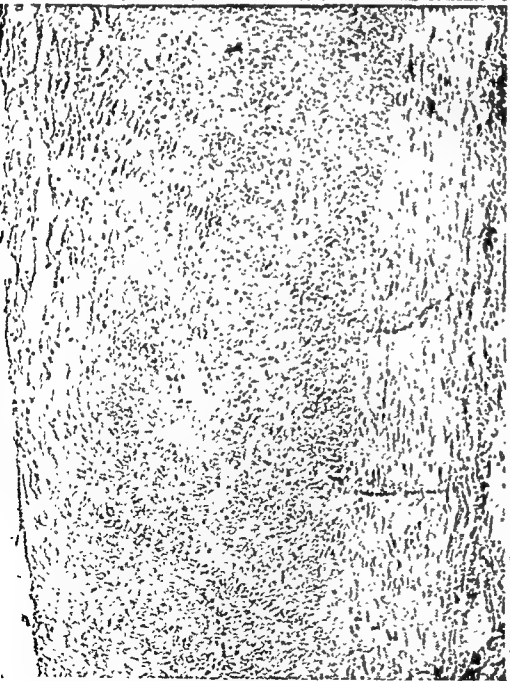


Fig. 15.



of the first two decades, in two of 10 patients of the third decade, in 6 of 10 of the fourth decade and in 7 of 9 in the fifth decade. Fibrosis of the media was found in 3 of 9 in the fifth decade. Infiltration of mononuclear cells was found in 1 case in the fourth decade. Venous thrombosis was found in only one case, a fifty-eight-year-old white man dead of lobar pneumonia. Gross sclerosis of the coronaries was found in none of the 5 cases of the first two decades where notation was made, in 2 of 5 of the third decade, in 2 of 5 of the fourth decade, in 4 of 5 of the fifth and sixth decades.

Edema is constant in the rheumatic coronaries and in the controls. In both series it is probably due to the presence of infectious disease, circulatory disturbance or both, and is obviously more common in the media than elsewhere. We agree with Segre and Kellner (1921-22) that it is not post-mortem artefact. It is probable that it is in some way related to chromotropic substance. In the control cases chromotropic change was not found in the coronary arteries, but it was observed in more than half of the rheumatic cases. If sections be stained lightly with hematoxylin, it escapes notice and requires heavy hematoxylin staining or staining with polychrome methylene blue or preferably with thionin. These special methods were not used in all cases, and the data here given cannot be regarded as exact. Nevertheless the factor of error is probably much the same throughout, and it seems justifiable to state that chromotropic substance is frequent in the rheumatic coronaries. Cellina (1933) stated that in the aorta chromotropic substance increases as age advances and considered it an age phenomenon rather than the result of pathological change. In our rheumatic coronaries it is almost equally common at all ages. It cannot therefore, in this situation, be an age process alone and is regarded as definitely pathological. That it is more common in rheumatic fever than in other severe infectious diseases is not established by these studies.

The interpretation of exactly what constitutes fibrinoid is not set down by those who have reported on it. For the purpose of this study it has been considered to be an intensely acidophilic substance, arranged in fibrillar fashion sometimes with beading at intersections. It was observed in many of the controls but was found in all the rheumatic cases. It was seen most frequently in the media, but was common in the intima and was found also in the adventitia. There is little doubt as pointed

PLATE IV

- Fig. 13.—Marked fibrosis of intima of large coronary artery. Male, aged twenty-four years. Hematoxylin and eosin. Wratten green filter B-58. $\times 65$.
 Fig. 14.—Marked intimal sclerosis eccentrically situated in large coronary artery. Male, aged nineteen years. Hematoxylin and eosin. Wratten green filter B-58. $\times 17$.
 Fig. 15.—Nodular intimal fibrosis of a small intramural coronary artery. Female, aged fourteen years. Hematoxylin and eosin. Wratten green filter B-58. $\times 200$.
 Fig. 16.—Irregular intimal and medial fibrosis with "hyaline scarring" of media in a medium-sized intramural coronary artery. Female, aged forty-three years. Hematoxylin and eosin. Wratten green filter B-58. $\times 120$.

out previously that fibrinoid is most frequent in arteries the seat of the supposedly allergic disturbances, but our control cases and the reports of Henschen (1927) indicate that it may be found in other conditions.

Necrosis was constant in the controls and appeared to be more frequent in the rheumatic series as age increases. The control observations nullify those of the rheumatic cases.

Swelling of elastica was frequent in both rheumatic and control cases. Fragmentation and splitting did not occur in the controls until the age of twenty-four years. In the rheumatic cases of the first decade these more severe elastica changes were found in 66 per cent and in the second decade in 58 per cent. Thus it is apparent that severe elastica alterations occur earlier than in the controls. Furthermore the simpler change, swelling, was found to be much more frequent in the rheumatic arteries of the first two decades than in the controls. We have no observations to confirm or contradict the report of Wiesel (1906) that some infections injure the elastica more severely than do others, but can state that rheumatic fever produces early and serious damage to elastica of the coronary arteries.

Aschoff nodules were found to involve the adventitia in about equal percentages at all ages. In the younger individuals they were richly cellular, often with extensive necrosis, but in later life were more fibrous, less frequent in the individual case and often identified with difficulty. In only 4 cases did they extend into the media. We found no evidence that they originate in media. In only rare instances could apparent compression of the vessel be found, but this requires fortunate line of section of a thin-walled artery, and the incidence may be somewhat greater in actual fact than our observations indicate. In no case was complete occlusion by Aschoff nodules observed. The significance of the Aschoff nodules in the arterial walls is that of involvement of the coronary tree in the special type of rheumatic inflammation with the implication of permanent damage. In our opinion the compression of coronary arteries by Aschoff nodules has little if any influence upon the circulation within.

The infiltration into the adventitia of large mononuclear cells, evidently histiocytic in general character, and of those with the morphology of small lymphocytes and plasma cells, was frequent and practically constant after the third decade. This was found in only one of the controls. It is apparently a part of the rheumatic inflammatory reaction and, while not morphologically specific, constitutes part of that picture, drawn by Klinge, of collagenous swelling, fibrinoid degeneration and hyaline scarring to be found in hyperergic reactions. It extended into the media in only 7 cases. Polymorphonuclear leucocytes played only a small part. In 5 cases of the first decade they were found in the adventitia of medium-sized vessels and extended into the intima in one

of these. In one case of the second decade (nineteen-year-old white male) cells were found in the intima of a large coronary, but they could not be positively identified as polymorphonuclear leucocytes. In one case each of the third and fourth decades polymorphonuclear leucocytes were found in the intima of large coronaries. It will probably be necessary to use oxidase stains on suitable material to determine how great a part the polymorphonuclear leucocytes actually play.

The occurrence of ante-mortem blood clots in the vessels has been referred to here as thrombosis. In the smaller vessels it was often occlusive, but in several larger vessels it occurred as a mural lesion. Some were rich in white blood cells, especially leucocytes; others were almost wholly fibrin; and there were mixtures. They occurred both with and without endocarditis lenta. They are interpreted as part of the vascular lesion rather than as emboli. This is in accord with the fact that the controls showed practically no inflammatory lesions of the arteries and in only one case thrombosis. It is not clear that bacteria produce the thrombosis, because in many cases the blood was apparently sterile. The only organisms recovered in cases with thrombosis were streptococci, but in our cases of streptococcemia only half showed thrombosis. That thrombosis is more frequent in rheumatic coronaries than in those of other severe infections is not established.

Although the various forms of intimal disease described by other writers have been observed, attention has been centered on fibrosis. Special stains for fat in numerous instances have demonstrated it in the thickened intima of some of the large coronaries but have been negative in the smaller divisions. Generally the intimal fibrosis in both large and small coronaries has been nodular rather than diffuse. Even in older patients, where extensive fibrosis is often present, it has shown nodular augmentation. Microscopically fibrosis was more often observed in the smaller arteries than in the main stems, and this corresponds to the infrequency of gross sclerosis of the large coronaries in the reports of others and ourselves. By the end of the first decade more than two-thirds of the cases showed under the microscope intimal fibrosis of the smaller vessels. In the second decade 92 per cent exhibited it, and in the third and subsequent decades it was present in all cases. Medial and adventitial fibrosis are more difficult to detect and occur less frequently. The controls showed intimal fibrosis in 1 of 9 cases of the first decade, none in the second, 2 of 10 in the third, 6 of 10 in the fourth and all those of the subsequent decades. Medial and adventitial fibrosis were not found in the controls before the fifth decade. Thus it is apparent that permanent disease appears in the coronary arteries early in the course of rheumatic fever. Our results are in general conformity with those of Zeek (1932) in that gross sclerosis of the coronaries is pre-co-

cious. Microscopically intimal fibrosis is more frequent than would be indicated by the gross examination.

The nature of the intimal fibrosis is uncertain. The fact that it increases in incidence as age advances indicates that it is progressive and not merely cicatrization or substitution. It is probable that the same is true of rheumatic endocardial and pericardial lesions. Thus the intimal lesions are closely correlated with the other lesions of serous membranes of this disease. Many regard arteriosclerosis in general as of inflammatory character. If this be true, the intimal fibrosis is in the same category.

No evidence was brought out by our observations that regeneration of medial muscle occurs in the course of the arterial disease.

Special attention was not given to the frequency of involvement of arteries other than the coronaries in the rheumatic process, but what have been described as typical lesions in the aorta and pulmonary artery were frequent.

The acute lesions of coronary arteries go hand in hand with acute lesions of the myocardium. The latter are destructive and lead to scarring. The amount of scarring increases with age. This might be thought of as a progressive fibrosis, but with it there are larger and larger areas of muscle destruction, which could hardly be secondary to the fibrosis. Thus the increasing amount of muscle destruction and fibrosis must be due either to recurring acute cycles of rheumatic fever or to chronic arterial disease. Many cases, if the history can be depended upon, are monocyclic. Extensive myocardial fibrosis in these cases can better be explained by chronic arterial disease than otherwise. This leads to the conclusion that the significant arterial lesion for chronic fibrosis of the myocardium is the intimal fibrosis of the smaller branches, a view in accord with that of Brown (1932) as regards myocardial fibrosis in general. Thrombosis can be attributed in most cases either to bacteremia or circulatory failure. When it occurs it is not widespread and neither in the fresh nor cicatrized stage could account for the extensive myocardial fibrosis.

CONCLUSIONS

1. Rheumatic fever regularly produces disease of the coronary arteries. Either inflammatory or fibrotic lesions or both are practically constant. Except for participation by Aschoff nodules, the lesions are not specific for rheumatic fever. Fibrinoid degeneration is suggestive but not diagnostic. Elastica degeneration appears to be especially severe.

2. The coronary disease is irregularly distributed as to both the various divisions of the coronary tree and the individual members affected. Its relation to myocardial disease cannot be positively established, but the late myocardial fibrosis is greater than is to be expected

from the early acute myocarditis alone. The influence of the coronary disease upon myocardial fibrosis is better explained by intimal fibrosis than otherwise.

3. Rheumatic fever predisposes to fibrosis of the coronary arterial tree in early life and to what appears to be precocious coronary sclerosis; but, although this is probably a chronic inflammation, it has not been shown conclusively to be dependent upon the acute degenerative and inflammatory lesions.

4. The coronary arteries in rheumatic fever undergo a progressive sequence of inflammatory lesions which closely resemble those of the endocardium and pericardium. It is practically certain that severe myocardial damage is associated with the arterial disease. The resulting effect upon myocardial efficiency appears to be of significance in the clinical management and prognosis of rheumatic heart disease.

REFERENCES

- Apitz, K.: Ueber anaphylaktische Organveränderungen bei Kaninchen, *Virchows Arch. f. path. Anat.* 289: 46, 1933.
- Idem: Ueber die Gefäßwandungsschädigung durch Crotalusgift, *Centralbl. f. allg. Path. u. path. Anat.* 57: 273, 1933.
- Aschoff, L.: Zur Myokarditisfrage, *Verhandl. d. deutsch. path. Gesellsch.* 8: 46, 1904.
- Idem: Discussion of paper by Lüpke on Periarteriitis nodosa, *Verhandl. d. deutsch. path. Gesellsch.* 10: 157, 1906.
- Idem, and Tawara, S.: Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwäche, Jena, 1906, Gustav Fischer.
- Astier: Quoted by Rabé.
- Barnard, W. G.: Diffuse and Nodular Fibrosis of Adventitia of Aorta (rheumatic periaortitis), *J. Path. & Bact.* 32: 95, 1929.
- Besangon, F., and Weil, M. P.: La dissociation auriculo-ventriculaire é les arrhythmies d'origine rhumatismale, *Ann. de méd.* 19: 167, 1926.
- Besangon, F., and Weil, M. P.: L'Aortite rhumatismale, *Ann. de méd.* 19: 175, 1926.
- Bloom, W.: Development of Elastic Fibers in Cultures of Embryonic Heart Muscle, *Proc. Soc. Exper. Biol. & Med.* 26: 779, 1929; Studies in Fibers in Tissue Cultures. II. The Development of Elastic Fibers in Cultures of Embryonic Heart and Aorta, *Arch. f. exper. Zellforsch.* 9: 6, 1929.
- Brown, M.: A Study of the Pathogenesis of Myocardial Fibrosis ("Chronic Fibrous Myocarditis"), *Am. J. M. Sc.* 184: 707, 1932.
- Breitenecker, L.: Suspected Poisoning; Death From Rheumatic Aortitis, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 18: 312, 1931; Abstract: *Arch. Path.* 15: 311, 1933.
- Cellina, M.: Sul comportamento della sostanza mucoide dell'aorta negli stati infettivi acuti e cronici, *Cuore e circolaz* 15: 506, 1931. Abst.: *Centralbl. f. allg. Path. u. path. Anat.* 56: 342, 1933.
- Chiari, H.: Ueber Veränderungen in der Adventitia der Aorta und ihrer Hauptäste im Gefolge von Rheumatismus, *Beitr. z. path. Anat. u. z. allg. Path.* 80: 336, 1928.
- Idem: Ueber Veränderungen in der Arteria pulmonalis in Fällen von akuter rheumatischer Endocarditis oder bei Herzfehler rheumatischen Ursprungs, *Klin. Wchnschr.* 9: 1862, 1930.
- Idem: Ueber Veränderungen in der Arteria pulmonalis in Fällen von Rheumatismus, *Beitr. z. path. Anat. u. z. allg. Path.* 88: 1, 1931.
- Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, *Am. J. Dis. Child.* 45: 933, 1933.
- Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* 39: 1, 1924.
- Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, *AM. HEART J.* 5: 705, 1930.

- Coombs, C.: The Myocardial Lesions of the Rheumatic Infection, *Brit. M. J.* 2: 1513, 1907.
- Idem: Rheumatic Myocarditis, *Quart. J. Med.* 2: 26, 1908-09.
- Idem: The Histology of Rheumatic Carditis and Other Rheumatic Phenomena, *Brit. M. J.* 1: 620, 1911.
- Coombs, C. F.: Rheumatic Heart Disease, New York, 1924, William Wood & Co.
- Cowan, J. M.: The Heart in Acute Disease, *J. Path. & Bact.* 9: 87, 1904.
- Craciun, E. C., Visineanu, N., Gingold, N., and Ursu, A.: Les lésions histologiques de la maladie de Bouillaud. Leur valeur biologique, *Ann. d'Anat. Path.* 10: 157, 1933.
- Dawson, M. H.: A Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis, *J. Exper. Med.* 57: 845, 1933.
- De Mussy: Quoted by Rabé.
- Eiman, J., and Gouley, B. A.: Rheumatic Pneumonitis, *Arch. Path.* 5: 558, 1928.
- Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, *Deutsch. Arch. f. klin. Med.* 134: 366, 1920.
- Idem: Beiträge zur Frage der Herz- und Gelenkveränderungen bei Gelenkrheumatismus und Scharlach, *Virchows Arch. f. path. Anat.* 232: 134, 1921.
- Idem: Zur Frage der Polymyositis (Dermatomyositis), *Arch. f. Dermat. u. Syph.* 130: 1, 1921.
- Idem: Vergleichende Herzuntersuchungen bei Scharlach, Streptokokkeninfektion und rheumatischer Granulomatose, *Beitr. z. path. Anat.* 85: 445, 1930.
- Frothingham, C.: The Relation Between Acute Infectious Diseases and Arterial Lesions, *Arch. Int. Med.* 8: 153, 1911.
- Gallivardin, L.: A l'étude de la myocardite rhumatismale, à propos d'un fait de myocardite interstitielle avec douleurs précordiales atroces, accès de tachycardie paroxystique et mort rapide sans asystole chez un enfant de 7 ans, *Lyon méd.* 110: 753, 1908.
- Gastewa, Z. A.: Ueber Arterienveränderungen bei Bauchtyphus, *Virchows Arch. f. path. Anat.* 289: 636, 1933.
- Geipel, P.: Ueber Myokarditis und Veränderung der quergestreiften Muskeln bei Rheumatismus, *München. med. Wchnschr.* 56: 2469, 1909.
- Gerstel, G.: Ueber die Veränderungen der Lungenblutgefäße bei Staublungen-erkrankten, Jena, 1933, Gustav Fisher; Heft 35, Veröffentlichungen aus der Gerwerbe- und Konstitutions-pathologie.
- Giraldi, J. J.: The Histology of the Aortic Wall in Acute Rheumatism, *Bristol Med.-Chir. J.* 46: 145, 1929.
- Gouley, B. A., Bellet, S., and McMillan, T. M.: Tuberculosis of the Myocardium: Report of Six Cases With Observations on Involvement of Coronary Arteries, *Arch. Int. Med.* 51: 244, 1933.
- Gräff, S.: Pathologische Anatomie und Histologie des Rheumatismus infectiosus, in Rheumaprobleme, Gesammelte Vorträge gehalten auf dem I. Aerztekursus des Rheuma-Forschungs-Instituts am Landesbad der Rheinprovinz in Aachen, Leipzig, 1929, Georg Thieme.
- Gray, S. H., and Aitken, L.: Late Gross Lesions in the Aorta and Pulmonary Artery Following Rheumatic Fever, *Arch. Path.* 8: 451, 1929.
- Gruber, G. B.: Zur pathologischen Anatomie der Periarteriitis nodosa, *Virchows Arch. f. path. Anat.* 245: 123, 1923; Zur Frage der Periarteriitis nodosa, mit besonderer Berücksichtigung der Gallenblasen- und Nieren-Beteiligung, *Ibid.* 258: 441, 1925.
- Hanot, V.: Considerations générales sur le rhumatisme articulaire aigu, *Presse méd.* 2: 171, 1894.
- Hansmann, G. H., and Schenken, J. R.: Melitensis meningo-encephalitis. Mycotic aneurysm due to *Brucella melitensis* var. porcine, *Am. J. Path.* 8: 435, 1932.
- Hayem, G.: Recherches sur les rapports existant entre la mort subite et les altérations vasculaires du coeur dans la fièvre typhoïde, *Arch. de physiol. norm. et path.* 2: 699, 1869.
- Idem: Études sur les myosites symptomatiques, *Arch. de physiol. norm. et path.* 3: 422, 473, 569, 1870.
- Henschen, F.: Ueber eine eigenartige mit Thrombenbildung verbundene Reaktion des Gefässendothels, *Acta. med. Scandinav.* 65: 539, 1927.
- Huguenin, P.: Contribution à l'étude de la myocardite infectieuse diphthérique, *Rev. de méd.* 8: 790, 995, 1883.

- Jäger, E.: Zur pathologischen Anatomie der Thromboangiitis obliterans bei juveniler Extremitätengangrän, Mitt. I. and II, Virchows Arch. f. path. Anat. 284: 526, 584, 1932.
- Idem: Zur histologischen Ausheilung der Periarteriitis nodosa und deren Beziehung zur juvenilen Atherosklerose, Virchows Arch. f. path. Anat. 288: 833, 1933.
- Jores, L.: Arterien, Henke Lubarsch Handbuch der spez. path. Anat. u. Hist., Berlin, 1924, Vol. II, p. 646, Julius Springer.
- Kahn, M. H.: Etiologic Factors in Angina Pectoris. An Analysis of Eighty-Two Cases in Private Practice, Am. J. M. Sc. 172: 195, 1926.
- Kerr, W. J., Larkey, S. V., and Larsen, A. E.: Coronary Occlusion and Myocardial Degeneration, California & Western Med. 23: 46, 1925.
- Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus. I. Mitteilung. Das rheumatische Frühinfiltrat. (Akutes degenerativ-exsudatives Stadium), Virchows Arch. f. path. Anat. 278: 438, 1930; II. Mitteilung. Das subakut-chronische Stadium des Zellknötchens, Ibid. 279: 1, 1931; Der Rheumatismus. Pathologisch-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für das ärztliche Rheumaproblem, Ergebn. d. allg. Path. u. path. Anat. 27: 1, 1933.
- Idem, and Vaubel, E.: Das Gewebsbild des fieberhaften Rheumatismus. IV. Die Gefäße beim Rheumatismus, insbesondere die "Aortitis rheumatica" (mit Betrachtung zur Ätiologie des fieberhaften Rheumatismus vom pathologisch-anatomischen Standpunkt), Virchows Arch. f. path. Anat. 281: 701, 1931.
- Klinger, H.: Grenzformen der Periarteriitis nodosa, Frank. Ztschr. f. Path. 42: 455, 1931.
- Klotz, O.: Rheumatic Fever and the Arteries, Tr. A. Am. Physicians 27: 181, 1912.
- Idem: Nodular Endarteritis of the Aorta About the Intercostal Arteries, J. M. Research 31: 409, 1914-15; Fatty Degeneration of the Intima of Arteries, Ibid. 32: 27, 1915.
- Idem: Concerning the Pathology of Some Arterial Diseases, Ann. Int. Med. 4: 814, 1926.
- Idem, and Lloyd, W.: Sclerosis and Occlusion of the Coronary Arteries, Tr. A. Am. Physicians 45: 108, 1930.
- Krehl, L.: Beitrag zur Pathologie der Herzklappenfehler, Deutsch. Arch. f. klin. Med. 46: 454, 1890.
- Krompecher, S.: Telangiostenose, die morphologische Grundlage der "juvenilen" oder "spontanen" Gangränen (Endarteriitis obliterans, Arteriitis obl., Thromboangiitis obl.), Arteriosclerosis renum und Skleroderma, Beitr. z. path. Anat. u. z. allg. Path. 85: 647, 1930.
- Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated With Rheumatic Cardiac Disease, Arch. Path. 6: 247, 1928.
- Landouzy, L., and Siredey, A.: Contribution à l'histoire de l'arterite typhoïdique, Rev. de méd. 5: 843, 1885.
- Landouzy, L., and Siredey, A.: Étude des localisations angiocardiaques typhoïdiques, etc., Rev. de méd. 7: 804, 919, 1887.
- Laubry, C., Huguenin, R., Casteran, R., and Albot, G.: Aortite chronique et myocardite pseudo-gommuilaire d'origine vraisemblablement rhumatismale, Ann. d'anat. path. 7: 614, 1930.
- Legroux: Quoted by Rabé.
- Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, Medicine 8: 245, 1929.
- Levy, R. L., and Turner, K. B.: Impaired Auriculoventricular Conduction in Rheumatic Fever, Arch. Int. Med. 43: 267, 1929.
- Lillie, R. D.: Pathology of the Eastern Type of Rocky Mountain Spotted Fever, U. S. Public Health Reports 46: 2840, 1931 (Reprint No. 1516).
- Lisi, F.: Aneurisma metastatico settico dell'arteria epatica, Arch. Ital. di anat. e.istol. pat. 1: 92, 1930.
- Lukowski, P.: Elektrokardiographische Beobachtungen bei akutem Rheumatismus, Deutsches Arch. f. klin. Med. 174: 268, 1932.
- Idem: Elektrokardiographische Beobachtungen bei Abdominaltyphus und Pneumonie, Deutsches Arch. f. klin. Med. 174: 587, 1933.
- MacCallum, W. G.: Rheumatism, J. A. M. A. 84: 1545, 1925.
- Idem: Acute and Chronic Infections as Etiological Factors, Arteriosclerosis. A Survey of the Problem. Publication of the Josiah Macy, Jr., Foundation, edited by E. V. Cowdry, New York, 1933, p. 355, The Macmillan Co.

- MacLean, D. L.: Sclerosis of the Coronary Arteries of the Heart, *Ann. Int. Med.* 2: 1253, 1929.
- Mandelstamm, M.: Ueber die Eigentümlichkeiten der Gefäßveränderungen bei sog. chirurgischer Tuberkulose, *Virchows Arch. f. path. Anat.* 287: 429, 1932.
- Martin, H.: Recherches sur la nature et la pathogénie des lésions viscérales consécutives à l'endartérite oblitérante et progressive (scléroses dystrophiques), *Rev. de méd.* 1: 369, 1881.
- Idem: Recherches sur la pathogénie des endocarditis et des scléroses cardiaques, *Rev. de méd.* 3: 81, 1883, section on Affections aiguës du cœur d'origine vasculaire, p. 103.
- McClenahan, W. W., and Paul, J. R.: A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever, *Arch. Path.* 8: 595, 1929.
- McMeans, J. W.: The Splitting of the Elastic Fibers in Arteries, *J. M. Research* 32: 377, 1915.
- Metz, W.: Die Geweblichen Reaktionserscheinungen an der Gefäßwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteriitis nodosa, *Beitr. z. path. Anat. u. z. allg. Path.* 88: 17, 1931.
- Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, *Am. J. Path.* 8: 717, 1932.
- Oettinger, I., and Neslin, W.: Ueber atrioventrikuläre Automatie bei rheumatischer Karditis, *Deutsches Arch. f. klin. Med.* 173: 212, 1932.
- Ophüls, W.: Periarteritis Acuta Nodosa, *Arch. Int. Med.* 32: 870, 1923.
- Pappenheimer, A. M., and Von Glahn, W. C.: Lesions of the Aorta Associated With Acute Rheumatic Fever, and With Chronic Cardiac Disease of Rheumatic Origin, *J. M. Research* 44: 489, 1923-24.
- Pappenheimer, A. M., and Von Glahn, W. C.: Studies in the Pathology of Rheumatic Fever. Two Cases Presenting Unusual Cardiovascular Lesions, *Am. J. Path.* 3: 583, 1927.
- Parkinson, J., Gosse, A. H., and Gunson, E. B.: The Heart and Its Rhythm in Acute Rheumatism, *Quart. J. Med.* 13: 363, 1919-20.
- Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* 7: 383, 1928.
- Perry, C. B.: The Main Branches of the Coronary Arteries in Acute Rheumatic Carditis, *Quart. J. Med.* 23: 241, 1929-30.
- Rabé, M.: Contribution à l'étude des lésions des artères dans l'infection rhumatismale, *Presse méd.* 10: 927, 1902.
- Ramsey, E. M., and Alpert, L. K.: Response of tissue of the intima to injurious agents, *Proc. Soc. Exper. Biol. & Med.* 30: 1433, 1933.
- v. Romberg, E.: Ueber die Bedeutung des Herzmuskels für die Symptome und den Verlauf der akuten Endocarditis und der Chronischen Klappenfehler, *Deutsches Arch. f. klin. Med.* 53: 141, 1894.
- Rössle, R.: Zum Formenkreis der rheumatischen Gewebsveränderungen, mit besonderer Berücksichtigung der rheumatischen Gefässentzündungen, *Virchows Arch. f. path. Anat.* 288: 780, 1933.
- Sacks, B.: The Pathology of Rheumatic Fever. A Critical Review, *AM. HEART J.* 1: 750, 1925-26.
- v. Sántha, K.: Ueber Gefäßveränderungen im Zentralnervensystem bei Chorea rheumatica, *Virchows Arch. f. path. Anat.* 287: 405, 1932.
- Scharpf, A.: Ueber das Verhalten der Gefäße bei akuten Infektionskrankheiten, *Frank. Ztsch. f. Path.* 2: 391, 1909.
- Schenken, J. R., and Hansmann, G. H.: Vascular Lesions of the Gastrointestinal Tract in Mercury Poisoning, *Arch. Path.* 14: 152, 1932.
- Schultz, A.: Pathologie der Blutgefäße, *Lubarsch-Ostertag Ergebn. d. allg. Path.* 221: 207, 1927.
- Schulz, M., and Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus. XIII. Mitteilung. Aortitis rheumatica und Arteriosklerose, *Virchows Arch. f. path. Anat.* 288: 717, 1933.
- Segre, R., and Kellner, E.: Ueber die sogen. ödematöse Durchtränkung der Arterienwand, *Centralbl. f. allg. Path.* 32: 561, 1921-22.
- Seifried, O., and Cain, C. B.: Histological Studies of Hog Cholera. II. Lesions of the Vascular System, *J. Exper. Med.* 56: 345, 1932.
- Semsroth, K., and Koch, R.: Ueber Gefäßläsionen bei Allgemeininfektion (Ein Beitrag zur Genese der Periarteriitis nodosa), *Krankheitsforschung* 8: 191, 1930.

- Siegmund, H.: Ueber nicht syphilitische Aortitis (Pathologisch-Anatomische Demonstration zur Frage der Gefässveränderungen bei Allgemeininfektionen), *Ztschr. f. Kreislaufforsch.* 21: 389, 1929.
- Slater, S. R.: The Involvement of the Coronary Arteries in Rheumatic Fever, *Am. J. M. Sc.* 179: 22, 1930.
- Smith, H. L., and Bartels, E. C.: Coronary Thrombosis With Myocardial Infarction and Hypertrophy in Young Persons, *J. A. M. A.* 98: 1072, 1932.
- Stoerk, O., and Epstein, E.: Ueber arterielle Gefässveränderungen bei Grippe, *Frank. Ztschr. f. Path.* 23: 163, 1920.
- Stolkind, E. J.: Angina Pectoris in Children, *Brit. J. Child. Dis.* 25: 1, 1928.
- Sutton, D. C., and Lueth, H.: Diseases of the Coronary Arteries (Myocarditis), St. Louis, 1932, The C. V. Mosby Co.
- Swift, H. F.: The Pathogenesis of Rheumatic Fever, *J. Exper. Med.* 39: 497, 1924.
- Swift, H. F.: The Heart in Infection, *AM. HEART J.* 3: 629, 1928.
- Swift, H. F., and Hitchcock, C. H.: Cardiac Pain in Rheumatic Fever, *J. A. M. A.* 90: 678, 1928.
- Swift, H. F., Derick, C. L., and Hitchcock, C. H.: Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, *Tr. A. Am. Physicians* 43: 192, 1928.
- Takayasu, R.: Zur Kenntniss der sogenannten Endarteriitis infectiosa und der Knötchenbildung bei rheumatischer maligner Endokarditis, *Deutsches Arch. f. klin. Med.* 95: 270, 1909.
- Therese: Quoted by Sutton & Lueth.
- Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* 2: 235, 1926.
- Wätjen: Ein besonderer Fall rheumatischer Myokarditis, *Verhandl. d. deutsch. path. Gesellsch.* 18: 223, 1921.
- Wearn, J. T.: Thrombosis of the Coronary Arteries With Infarction of the Heart, *Am. J. M. Sc.* 165: 250, 1923.
- White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *AM. HEART J.* 3: 302, 1928.
- White, P. D., and Mudd, S. G.: Angina Pectoris in Young People, *AM. HEART J.* 3: 1, 1927.
- Wiesel, J.: Ueber Erkrankungen der Koronararterien in Verlaufe akuter Infektionskrankheiten, *Wien. klin. Wchnschr.* 19: 723, 1906.
- Wiesel, J.: Die "rheumatische" Infektion. I. Die akute Gelenkrheumatismus, *Med. Klin.* 19: 163, 1923.
- Wiesel, J., and Loewy, R.: Die Erkrankungen der peripheren Gefässe bei akuter und chronischer Kreislaufinsuffizienz, *Wien. klin. Wchnschr.* 32: 1083, 1919.
- Wiesner, R.: Ueber Veränderungen der Koronargefässe der Infektionskrankheiten, *Wien. klin. Wchnschr.* 19: 725, 1906.
- Zeek, P.: Studies in Atherosclerosis. II. Atheroma and Its Sequelae in Rheumatic Heart Disease, *Am. J. M. Sc.* 184: 356, 1932.

INCIDENCE AND SIGNIFICANCE OF ACTIVE INFECTION IN CASES OF RHEUMATIC CARDIOVALVULAR DISEASE DURING THE VARIOUS AGE PERIODS*†

A CLINICAL AND PATHOLOGICAL STUDY

M. A. ROTHSCHILD, M.D., M. A. KUGEL, M.D., AND LOUIS GROSS, M.D.
NEW YORK, N. Y.

IT IS not an infrequent clinical observation that in cases of rheumatic heart disease the degree of mechanical damage to the heart valves does not necessarily bear a definite relation to the occurrence and extent of heart failure. It was recognized by Krehl as early as 1889 that changes in the myocardium rather than the valvular defect were probably the immediate cause of cardiac failure. In an investigation of ten cases of cardiovalvular disease, chiefly in elderly people, Krehl¹ found fibrosis of the heart muscle, degenerative changes of the coronary arteries and cellular infiltrations in the myocardium. He attributed the diminished functional capacity of the heart to these changes. At this time he expressed the view that systematic studies of the myocardium in cases of valvular disease should be made.

Following the discovery by Aschoff of the specific myocardial lesion in the heart in rheumatic fever, additional attention was directed toward these inflammatory changes in the interpretation of myocardial failure. In general, however, it seems that the opinions expressed along these lines have been based solely on clinical impressions and isolated observations, rather than on an actual careful examination of autopsy material in a large series of cases with a systematic attempt to correlate the anatomical findings with the clinical observations. The present report represents an investigation of the clinical records and autopsy material from 161 cases of rheumatic cardiovalvular disease studied in the Mount Sinai Hospital, in an attempt to determine the incidence of myocardial disease and its relationship to myocardial failure.‡

Because of the uncertainty of clinical data, only those cases were included which presented anatomically and histologically unmistakable evidence of present or past rheumatic heart disease; viz., the presence

*From the Laboratories of the Mount Sinai Hospital, N. Y.

†Aided by a grant from the Lucius N. Littauer Foundation.

‡The terms "heart failure," "circulatory failure" and "myocardial failure" are used interchangeably in this report to indicate congestive failure observed clinically or confirmed by pathological examination. A patient is classified as being in congestive failure even though death may ensue from a complicating condition, such as bronchopneumonia or embolism.

of verrucous endocarditis on a markedly inflamed cusp, Aschoff bodies in the myocardium, the peculiar valvular deformity with its characteristic vascularization, certain types of ring lesions, and an old or recent auricular lesion. These cases were classified as active and quiescent according to the criteria to be described.

CASES WITH ACTIVE INFECTION

Needless to say, the question as to what constitutes activity of rheumatic infection in the heart may be answered quite properly in a number of ways. Grossly, the presence of a fresh pericarditis together with the characteristic verrucous endocarditis is generally considered evidence of activity. Further, the presence in the myocardium of lymphocytes, polymorphonuclear leucocytes, monocytes and swollen or necrotic collagen may be considered as additional signs of activity in a heart showing other unmistakable evidences of rheumatic infection. However, the presence of the Aschoff body in addition to these other findings is accepted as absolute proof of an active rheumatic infection. It is generally agreed not only that the presence of the Aschoff body indicates activity, but also that these lesions can be found in a very high percentage of active cases (Clawson,² Thayer,³ Kugel and Epstein,⁴ McClenahan and Paul,⁵ and others). In their studies of the standardized sections from rheumatic hearts, Gross, Antopol and Sacks⁶ found Aschoff bodies in 90 per cent of 40 hearts showing acute verrucous endocarditis. Thayer found Aschoff bodies in 87.5 per cent of 24 active cases, while McClenahan and Paul found them in 85 per cent of 28 fatal cases of active rheumatic fever.

In our series there were 106 cases which showed anatomical evidence of active infection. Aschoff bodies were found in 95 of these acute cases, an incidence of 89.6 per cent. In the remaining 11 active cases there was present either a fibrinous pericarditis, verrucous endocarditis, acute myocarditis or auricular lesions, but Aschoff bodies were not found after an extensive search.

QUIESCENT CASES

All cases showing the characteristic valvular deformity with or without evidences of old auricular lesions but without the presence histologically of swollen collagen, inflammatory cells, Aschoff bodies or a fibrinous pericarditis were placed in this group.

OUTLINE OF THE PROBLEMS

Having thus outlined our definitions of the type of material we used and our basis for judging of activity and quiescence, we wish to report in this paper first the incidence of quiescence and of active rheumatic myocarditis during the various age periods, and second, the significance of active infection and valvular deformities in their relation to myocardial failure.

With regard to the first problem, it is obvious that our statistics will depend, as do others, on the age of the patients, on the general incidence of the disease in the community from which this hospital draws its material, and on the relative difficulty with which autopsy permits are obtained from the various races which inhabit our wards. The ward service of the Mount Sinai Hospital consists of 500 beds for medical and surgical cases. One hundred of these are set aside for pediatrics. The hospital admits individuals of all ages and of various nationalities. Permission for autopsy examination was granted in a high percentage of cases, on the average 75 per cent in the past seven years. The incidence of autopsy permits was about equal in all age periods and for the various races represented. We may therefore assume that our statistics are a fair representation of the incidence of the disease in general in respect to age periods, bearing in mind the racial peculiarity of our patients and the local incidence of disease in the community.

In a series of 3,000 autopsies there were 180 cases with post-mortem evidence of rheumatic heart disease. As will be indicated in the text, a number of these patients died of conditions other than the past or present rheumatic infection. Complete anatomical investigation was made in 161 of these cases, and our report is based upon the findings in this group. Table I shows the age period incidence of active infection in these cases.

TABLE I
INCIDENCE OF ACTIVE INFECTION IN THE VARIOUS AGE PERIODS

AGE	TOTAL NO. STUDIED	ACTIVE CASES			QUIESCENT CASES		
		NUMBER	PER CENT	NO. DYING IN FAILURE	NUMBER	PER CENT	NO. DYING IN FAILURE
1-10	22	22	100	22	0	0	0
11-20	44	41	95	38	3	5	1
21-30	16	11	78	11	5	22	2
31-40	30	21	70	21	9	30	4
41-50	21	8	38	8	13	62	9
51-60	15	2	13	2	13	87	10
61-70	9	1	12	1	8	88	6
71-80	4	0	0		4	100	3
Total	161	106		103	55		35

CAUSE OF DEATH IN THE VARIOUS DECADES

Twenty-two individuals in this group of 161 cases died in the first decade of life. The youngest was an infant of seventeen months. The myocardium in all these 22 cases showed evidences of activity. In 20, Aschoff bodies were found. All succumbed to myocardial failure. The valvular defects on the whole were minimal. In some instances there was only a slight thickening and rolling of the anterior leaflet of the mitral valve or one of the aortic valve cusps. In three hearts

there was a slight stenosis of the mitral valve. In all these cases the degree of the mechanical defect was so slight that it obviously bore no relationship to the myocardial failure.

In the second decade there were 44 cases. Forty-one of these showed activity in the myocardium. In 37 of these, Aschoff bodies were found. Thirty-eight patients of these cases of acute rheumatic fever with myocarditis died of myocardial failure, or its complications. There were three active cases in which the patients did not die of myocardial failure. One had an extensive pulmonary tuberculosis; another died because of a *Streptococcus hemolyticus* bacteremia; the third died suddenly after an appendectomy, the underlying active rheumatic infection not being recognized clinically. In 35 of the 41 active cases in which the patients died of myocardial failure in which the degree of the valvular defect was studied, nine showed a tight mitral stenosis and two only a moderate valvular stenosis. In the remaining 24, the valvular defect apparently created no great mechanical hindrance to circulation. There were three patients who at the time of death showed no signs of active infection. One patient of these three quiescent cases succumbed to myocardial failure. The valvular defect in this instance was slight. The contributory cause for the myocardial failure was a severe anemia. The patients in the other two quiescent cases succumbed to pneumonia and typhoid fever, respectively.

The number of individuals with rheumatic heart disease dying between twenty and thirty years of age in this series is comparatively small. There were 16 cases, 11 of which showed an active myocarditis. In all of these, Aschoff bodies were found. In all 11 active cases the patients died of myocardial failure. In 3 of these a marked mitral stenosis was present; in 3 others the defect was moderate or slight. There were 5 quiescent cases in this group. Three of these showed no signs of myocardial failure, although in one instance there was a marked stenosis of the mitral and aortic valves. Empyema of the chest (*Streptococcus hemolyticus*), a postoperative infection and a purulent pneumonia, respectively, caused death in these instances. A fourth quiescent case, a boy of twenty-one years, presenting aortic insufficiency of long duration, gave a history of myocardial failure for seven years. This boy died suddenly, and upon autopsy there was found a well-marked aortic insufficiency and a markedly enlarged heart weighing 1,105 grams. There were no evidences of activity. The fifth quiescent case, a girl of twenty-four years, with mitral stenosis, gave a history of recurrent pulmonary edema associated with mental strain and excitement. She came to the hospital in acute pulmonary edema and at autopsy there were no signs of activity.

The fourth decade group presented some interesting clinical features. It is not uncommon to find individuals at this age without antecedent history of rheumatic infection develop circulatory failure for

the first time, although a well-marked mitral stenosis may be present, indicating that the valvular lesion had existed for a considerable time. The cause for the appearance of circulatory failure at this time is a matter for conjecture; although in several instances an active myocarditis with Aschoff bodies was found on histological examination. There were 30 deaths in this decade. Twenty-one of these 30 cases showed an active myocarditis. In 20 of these, Aschoff bodies were found. In all the cases in the fourth decade showing activity in the myocardium, the patients died of circulatory failure. The extent of the defect and the degree of stenosis of the valves were proportionately greater in this decade. In 12 instances the stenosis was marked, in 4 moderate, and in 4 slight. There were 9 quiescent cases. Four of these patients died of circulatory failure. In one there was coronary artery sclerosis and pulmonary embolism as the terminating cause of death; in another there were multiple pulmonary infarcts and emboli complicating a bronchitis and bronchopneumonia. In the third there was a severe secondary anemia (hemoglobin 18 per cent), while in the fourth case there were found no contributing causes for the myocardial failure. The degree of valvular defect was marked in only one of these. In the remaining 5 quiescent cases the patients died of the following causes: in two instances there was lobar pneumonia, in one a peritonitis, in another a postabortive sepsis, and in the fifth case, a carcinoma of the head of the pancreas. The valvular defects in this latter group were mild.

There were 21 individuals who died in the fifth decade. Eight showed evidence of activity, a surprisingly high incidence so late in life. In 6 of these, Aschoff bodies were found. In all 8 cases with evidence of active infection in the myocardium the patients succumbed to myocardial failure. Thirteen cases were quiescent. Nine of these patients died with evidences of myocardial failure and 4 of other causes. Thus, not only is there a sharp increase in the incidence of quiescent cases in this age period, but there is also an increased incidence in the number of quiescent cases in which the patients died of myocardial failure. A detailed analysis as to the cause of the failure in each quiescent case is of interest. Of the 9 quiescent cases in which the patients died of myocardial failure, hypertension and coronary atherosclerosis played a contributory rôle in 3 instances (two of these cases were further complicated by an occlusion of a coronary artery). Coronary thrombosis was the cause of death in a fourth case, while bronchopneumonia and pleurisy were present in a fifth case. The 4 remaining quiescent cases with evidences of congestive failure were terminated by bronchopneumonia in two instances and by cerebral emboli in the other two. The cause of death in the 4 quiescent cases in which the patients did not die in circulatory failure was as follows: carcinoma in two instances, acute

yellow atrophy in one, and renal and miliary tuberculosis in the other. There was no appreciable difference in the degree of mechanical defect in these groups.

Between the ages of fifty and sixty years there were 15 individuals who presented at necropsy evidence of rheumatic cardiovalvular disease past or present. In two of these, an active myocarditis with Aschoff bodies was found. In one of the active cases the patient died of a lobar pneumonia with some congestive failure, the other succumbed primarily to myocardial failure. In this latter instance, a man of fifty-one with a history of hypertension, there was found at autopsy a marked atherosclerosis of the coronary arteries with some evidence of an old occlusion. Ten patients of the 13 quiescent cases died of myocardial failure. Four of these showed emphysema complicated by chronic bronchitis, pulmonary infarction or coronary artery atherosclerosis. A long-standing hypertension with atherosclerosis of the coronary arteries was the contributing cause of failure in a fifth case, while in a sixth there was in addition a thrombosis of the left anterior descending coronary branch. In the two other quiescent cases in which the patients died of myocardial failure there was a marked aortic stenosis. Death occurred suddenly in both instances. One of these showed diffuse myocardial fibrosis and atherosclerosis of the coronary vessels. The ninth patient, a woman of fifty-three years, died following a cerebral embolism after a month of congestive failure with embolization to the bifurcation of the abdominal aorta. The patient in the tenth quiescent case of death with signs of congestive failure succumbed to a bronchopneumonia following an operation for the removal of an embolus from the brachial artery. There were 3 quiescent cases which presented no evidences of myocardial failure. All three patients died of carcinoma. In 10 of the 15 cases studied, the degree of the valvular defect was determined. In 7 of these there was a marked stenosis of the valves, while in 3 there was only a moderate valvular defect.

Nine individuals with rheumatic cardiovalvular disease survived until the seventh decade. Only one case in this entire group showed evidence of activity with Aschoff bodies in the myocardium. This patient, a woman of sixty-two years, showed in addition evidence of an old occlusion of a coronary artery and recent bronchopneumonia. She died of myocardial failure. Of the 8 quiescent cases, 6 patients had evidences of congestive failure. In two, arteriosclerosis of the coronary arteries was present, in one instance associated with myocardial fibrosis and in the other with hypertension. A third individual, aged sixty-five years, suffered from emphysema and chronic bronchitis and finally developed pneumonia. Three others, women of from sixty-five to sixty-seven years of age, showed some evidences of congestive failure but died of pneumonia complicating hypertension in two instances and chronic bronchitis in a third. There were two quiescent cases in which patients died of

causes other than heart failure—one died of erysipelas complicated by a streptococcus sepsis and the other of carcinoma.

There were 4 survivals in the eighth decade. In none of these was there any sign of active infection. The patients died of circulatory failure. In two of these coronary thrombosis was found, and in the third, in addition to infarctions of the lungs, there was found atherosclerosis of the coronary arteries with infarcts in the myocardium. In two cases the valvular defect was moderate; in the third there was a tight mitral stenosis. The oldest patient studied by us was a woman of eighty years with a tight mitral stenosis and a marked aortic stenosis. She died of a mesenteric artery thrombosis with no signs of myocardial failure.

DISCUSSION

The data presented above confirm the belief that neither the degree of myocardial failure nor its onset necessarily bears a relation to the severity of the valvular defect. A search for the inciting cause producing heart failure indicated that in the first five decades of life an active infection in the myocardium was found with significant frequency. Adults with tight mitral stenosis who are admitted to the hospital with circulatory failure and present no history of either symptoms or knowledge of a previous rheumatic infection not infrequently show on histological examination of the myocardium an active myocarditis of recent origin in a high percentage of the cases.

One hundred and six of the 161 cases studied showed active infection (Table I). In the first decade all of the 22 cases showed evidences of active rheumatic infection, in the second decade 95 per cent, in the third 78 per cent, and in the fourth 70 per cent. From the fifth to the eighth decades the percentage, although rapidly decreasing, is still unexpectedly high, ranging from 8 cases out of 21 (38 per cent) in the fifth decade, to 1 case out of 9 in the seventh decade. This indicates a remarkable persistence, or recurrence, of active rheumatic infection perhaps comparable to that seen in tuberculosis and syphilis.

One hundred and three of the 106 patients showing active lesions in the myocardium died of circulatory failure. Even with the most rigid criteria our studies show a striking correlation, if not an actual causal relationship between heart failure and activity. This is true of those patients dying of circulatory failure even as late as in the fifth decade. The relationship of active infection in bringing about a circulatory breakdown has already been recognized by Coombs⁷ and by Wilson and Kopel.⁸ In studying the significance of the leucocyte count as an index of rheumatic infection in children, Wilson and Kopel observed that a close correlation seemed to exist between the presence of a leucocytosis and a diminished vital capacity measurement in children with rheumatic heart disease. They feel that this further confirms the conception that

cardiac failure in these children is primarily due to infection rather than to mechanical factors. Coombs has expressed the belief that even in adults as late as thirty or forty years of age, the onset of dyspnea or myocardial failure may be traced to an active myocarditis which he frequently observed on microscopic examination in apparently quiescent cases.

While the causal relationship of active myocarditis to circulatory failure is very striking in the first two decades of life, it is not sufficiently appreciated that in cases of rheumatic heart disease in adults of the third, fourth and fifth decades of life a recurrent rheumatic myocarditis rather than the healed mechanical defects may in the majority of instances be the precipitating cause of the circulatory failure.

The clinical picture of the individuals dying of circulatory failure during the first decade did not vary materially from that of the individuals dying in the third and fourth decades, nor did the grade of circulatory failure differ in individuals in the first attack from that of those dying in a recurrent attack.

These observations apply not only to acute circulatory failure but especially to those cases of protracted circulatory failure which defy our usual therapeutic procedures. An individual in the first five decades of life with a chronic valvular defect whose myocardial efficiency is low, who has edema and a temperature varying from 99° to 100° for which no cause can be found, who does not respond to rest, digitalis and diuretics, and in whom no obvious precipitating cause of the myocardial failure can be discovered, should be suspected of having an active rheumatic infection as the underlying cause of his present failure. It is not uncommon to see such patients suddenly regain efficiency, especially when the signs of active infection have subsided, even when all therapeutic measures had previously failed.

On the other hand, it is true that not all individuals dying of circulatory failure showed active infection in the myocardium. As mentioned before, this parallelism of activity and myocardial failure is seen chiefly in those individuals dying in the first five decades of life.

It is equally important to point out that a number of individuals who have had rheumatic heart disease can become completely quiescent, reach the fifth, sixth, seventh and even the eighth decade of life and ultimately die of a totally unrelated disease without having any evidence during life of myocardial failure directly attributable to the mechanical defects of old rheumatic infection. (Table II.)

Absence of activity, which may be interpreted as quiescence or healing, has been found in this series of fatal cases as early as the second decade. Of the 161 cases investigated, 55 were quiescent. Table I shows the increasing percentage of quiescent cases in the later decades. This increasing incidence of quiescent cases occurs sharply in the fifth decade. Of the 55 quiescent cases studied, 35 patients died of myocardial

TABLE II

CAUSE OF DEATH IN CASES SHOWING NO EVIDENCE OF MYOCARDIAL FAILURE

AGE	SEX	ACTIVITY	CAUSE OF DEATH
13	M	Present	Acute otitis media, sigmoid sinus phlebitis, streptococcus sepsis.
15	M	None	Purulent bronchopneumonia.
17	M	None	Typhoid fever, hemorrhagic lobar pneumonia.
19	M	Present	Postoperative death following appendectomy.
19	F	Present	Extensive pulmonary and generalized tuberculosis.
22	F	None	Chronic pneumonia, streptococcus empyema of chest.
26	F	None	Purulent pneumonia.
30	M	None	Postoperative infection and hemorrhage.
34	F	None	Postabortive sepsis.
35	M	None	Peritonitis.
35	M	None	Lobar pneumonia.
37	F	None	Lobar pneumonia.
40	F	None	Carcinoma of pancreas.
48	M	None	Spongiblastoma in brain.
49	M	None	Carcinoma of bladder.
50	M	None	Generalized tuberculosis.
50	F	None	Acute yellow atrophy of liver.
51	M	None	Carcinoma of bladder.
59	F	None	Carcinoma of colon.
60	M	None	Carcinoma of pancreas.
63	M	None	Erysipelas, streptococcus sepsis.
67	F	None	Carcinoma of head of pancreas.
80	F	None	Mesenteric artery thrombosis.

failure or its complications. Twenty-eight of these were individuals older than forty years. The majority of those who died of circulatory failure in the sixth, seventh and eighth decades showed the contributory causes of heart failure to be expected at this age period, such as long-standing hypertension, coronary artery sclerosis, with occlusion at times, and long-standing pulmonary disease which increases the burden of the right heart. Individuals dying purely of the mechanical hindrance to the circulation due to the deformity of the valves were relatively few in number.

SUMMARY AND CONCLUSIONS

A clinical and pathological study of 161 persons dying with evidence of rheumatic heart disease, past or present, has been made in order to correlate chiefly the occurrence of myocardial failure, the degree of the valvular defects, and the presence of myocardial disease.

Of the 161 cases studied, 106 showed evidence of an active infection. One hundred and three patients of these 106 active cases died of circulatory failure. The occurrence of heart failure in the first five decades of life in individuals who have a valvular defect can, in the majority of instances, be attributed to an active infection of the myocardium rather than to the degree of the mechanical defect. It is striking to

note the high grade of mechanical defect existing in individuals living even to the fifth and sixth decade with little or no evidence of congestive failure.

In a few instances complete quiescence of the rheumatic myocarditis was present as early as the second decade of life. The number of the quiescent cases increased considerably in the later age periods. Circulatory failure in the later decades of life in individuals with valvular defects was found in the majority of cases to be precipitated by the expected contributory causes occurring at this time of life, viz., hypertension, either in the systemic or pulmonary circuit, atherosclerosis of the coronary arteries, coronary thrombosis, myocardial degeneration and fibrosis.

REFERENCES

1. Krehl, Ludolf: Beitrag zur Pathologie der Herzklappenfehler, *Deutsch. Arch. f. klin. Med.* 46: 454, 1889.
2. Clawson, B. J.: The Aschoff Nodule, *Arch. Path.* 8: 664, 1929.
3. Thayer, W. S.: Notes on Acute Rheumatic Disease of the Heart, *Bull. Johns Hopkins Hospital* 36: 99, 1925.
4. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated With Rheumatic Cardiac Disease, *Arch. Path.* 6: 247, 1928.
5. McClenahan, W., and Paul, J. R.: A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever, *Arch. Path.* 8: 595, 1929.
6. Gross, Louis, Antopol, Wm., and Sacks, Benjamin: A Standardized Procedure Suggested for Microscopic Studies on the Heart, *Arch. Path.* 10: 840, 1930.
7. Coombs, Carey F.: *Rheumatic Heart Disease*, New York, 1924, William Wood & Company.
8. Wilson, May G., and Kopel, M.: Significance of the Leukocyte Count as an Index of Rheumatic Infection in Children, *Am. J. Dis. Child.* 32: 46, 1926.

THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION

I. SEPTAL INFARCTS AND THE ORIGIN OF THE PRELIMINARY DEFLECTIONS OF THE CANINE LEVOCARDIOGRAM*

FRANK N. WILSON, M.D., IAN G. W. HILL, M.B.,† AND
FRANKLIN D. JOHNSTON, M.D.
ANN ARBOR, MICH.

INTRODUCTION

THIS article is the first of a series in which the changes in the form of the electrocardiogram observed after the ligation of the various subdivisions of the coronary arteries will be described. The experiments were carried out upon large dogs. In this animal the region supplied by the left coronary artery is much larger than that supplied by the right. A few millimeters from its origin the former vessel divides into three branches: the circumflex, the anterior descending, and the septal. The last nourishes a large part of the ventricular septum. When it is ligated, pronounced disturbances in intraventricular or in atrioventricular conduction usually occur. The anterior descending branch usually supplies most of the ventral wall of the left ventricle including the anterior papillary muscle, and those portions of the ventral wall of the right ventricle that lie near the interventricular sulcus. The circumflex branch usually supplies most of the dorsal wall of the left ventricle, including the posterior papillary muscle and the more apical portions of the dorsal wall of the right ventricle. The right coronary artery supplies the more basal portions of the wall of the right ventricle. There are of course numerous variations in the distribution of these vessels and their branches and in the manner in which they anastomose, so that the extent and the exact location of the infarct produced by ligating any one of them are variable.

The chief purpose of this paper is to describe and to discuss the three experiments in which the septal artery was ligated. In all of these complete right bundle-branch block developed, and we have therefore included here a description of the changes in the form of the levocardiogram observed after the ligation of other coronary arteries.

EXPERIMENTAL PROCEDURE

When we desired to study the immediate effects of coronary ligation, the animal was fully anesthetized with morphine and urethane and brought to the electrocardio-

*From the Department of Internal Medicine, University of Michigan Medical School.

†Of the Department of Medicine, University of Aberdeen.

graphic laboratory, where it was placed upon its back on a dog board. After beginning artificial respiration, the chest was opened by splitting the sternum. An incision parallel to the long axis of the heart was then made in the pericardium, and the cut edges were sewn to the margins of the chest wound so that the heart lay suspended as in a hammock. If the morphine given caused a pronounced slowing of the heart or a tendency to independent ventricular activity, the vagi were cut. For the standard electrocardiographic leads the electrodes were small copper disks with binding posts attached; these were sewn under the skin of the extremities. Similar electrodes were used for precordial leads, which were taken before the chest was opened.

When it was desired to study the late effects of infarction, the ligation operation was done in the surgical laboratories, and morphine and ether were used to induce anesthesia. A flap of skin and muscle in the precordial region was turned back, and the chest was opened by cutting through an intercostal space and retracting the adjacent ribs. A small incision in the pericardium gave access to the vessel selected. After this was tied, the chest was quickly closed layer by layer, and the animal was allowed to recover. Aseptic precautions were observed and infection was rare. No electrocardiograms were taken prior to, or immediately following, the operation. In making electrocardiographic observations after the desired interval had elapsed, the same plan was followed as in the experiments in which the immediate effects of coronary ligation were under investigation.

In ligating the septal artery we adopted the method employed by Lauterbach.¹ A complete description of this method and of the anatomical relations will be found in his article. This vessel is rather difficult to reach; it comes from the under side of the main trunk or the anterior descending branch of the left coronary artery very close to the junction of the anterior descending and circumflex branches. This junction is exposed by careful blunt dissection beneath the left auricular appendage in the angle between the attachment of this appendage and the pulmonary artery. A ligature is then passed first beneath the anterior descending branch close to its origin and then beneath the main trunk and beneath the circumflex branch in turn. When tied it is almost certain to catch the septal vessel. The dissection must be carried out with great care if uncontrollable hemorrhage is to be avoided.

DESCRIPTION OF SEPTAL EXPERIMENTS

The immediate effects of septal ligation were studied in only one animal (Experiment J). In less than two minutes after tying the ligature there was a slight elevation of the RS-T segment of the ventricular complex in Lead I and a pronounced depression of this segment in Lead III. These changes became slightly more conspicuous within the next few minutes (Fig. 1) and persisted. The first evidence of intraventricular block appeared one hour and forty-five minutes after the ligature was tied. At this time incomplete right bundle-branch block developed. Complexes characteristic of complete right branch block were observed about twenty minutes later. After a short period during which the block was at times incomplete no further change in the form of the electrocardiogram occurred. The animal was killed by inducing ventricular fibrillation about four hours after the septal artery was occluded. On opening the heart the infarct was faintly visible as a slightly discolored area, some 3 cm. in diameter, on the left side of the upper

septum. On palpation it was much firmer than the rest of the ventricular muscle. Both of the main subdivisions of the left bundle-branch crossed the affected area, which extended downward to the apex of the posterior papillary muscle and involved the upper three-fifths of the septal muscle. On the right side of the septum no change in the muscle was visible to the naked eye. Microscopic examination of the upper septum showed cloudy swelling and Zenker's necrosis, but no leucocytic infiltration or hemorrhage. No attempt to determine the condition of the bundle branches by histological examination was made in this or in our other experiments.

In two experiments the late effects of septal ligation were studied. In both of these the electrocardiographic observations were made forty-eight hours after tying the artery. In the first (Experiment 46) the

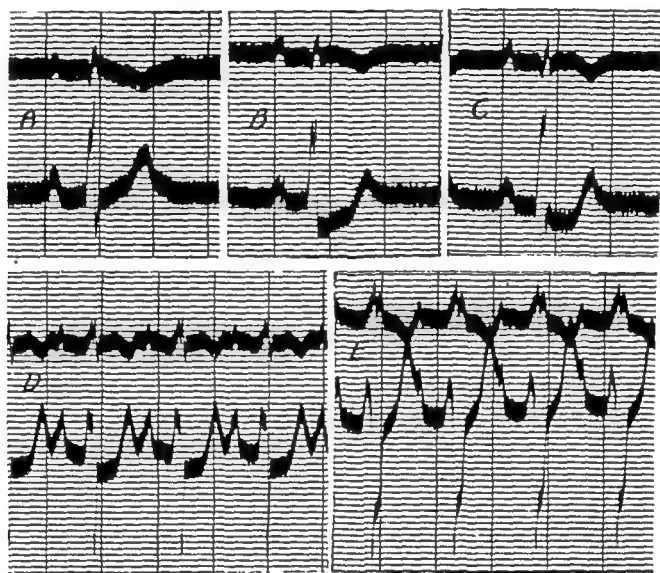


Fig. 1.—Experiment J. Lead I (above) and Lead III taken simultaneously just before and at various intervals after ligation of the septal branch of the left coronary artery. *A* was taken seven minutes before; *B*, three minutes after; *C*, forty-two minutes after; *D*, sixty-two minutes after; and *E*, two hours after tying this vessel.

standard leads taken before opening the chest showed complete right branch block, with ventricular complexes of unusual outline in Leads II and III (Fig. 2). A series of precordial leads was also taken. The exploring electrodes were sewn beneath the skin along a line passing across the precordium in a right-to-left and base-apex direction. This line intersected the midline 15.5 cm. below the episternal notch, and made an angle of about sixty-five degrees with the long axis of the body. The indifferent point paired with each exploring electrode in turn was a central terminal connected to the two fore legs and the left hind leg through resistances of 5,000 ohms.² In the curve taken farthest to the right the chief upstroke of QRS is late. It begins about 0.06 second after the first ventricular deflection in Lead I. In the curves from

the left side of the precordium the chief upstroke is early. It occurs about 0.02 second after the first deflection in Lead I. In these curves there is a conspicuous inverted peak synchronous with R in Lead I and a broad upward movement synchronous with S in Lead I. The midline curve is transitional in form, but the main upstroke is early. The precordial electrocardiograms are strikingly similar to those obtained in an

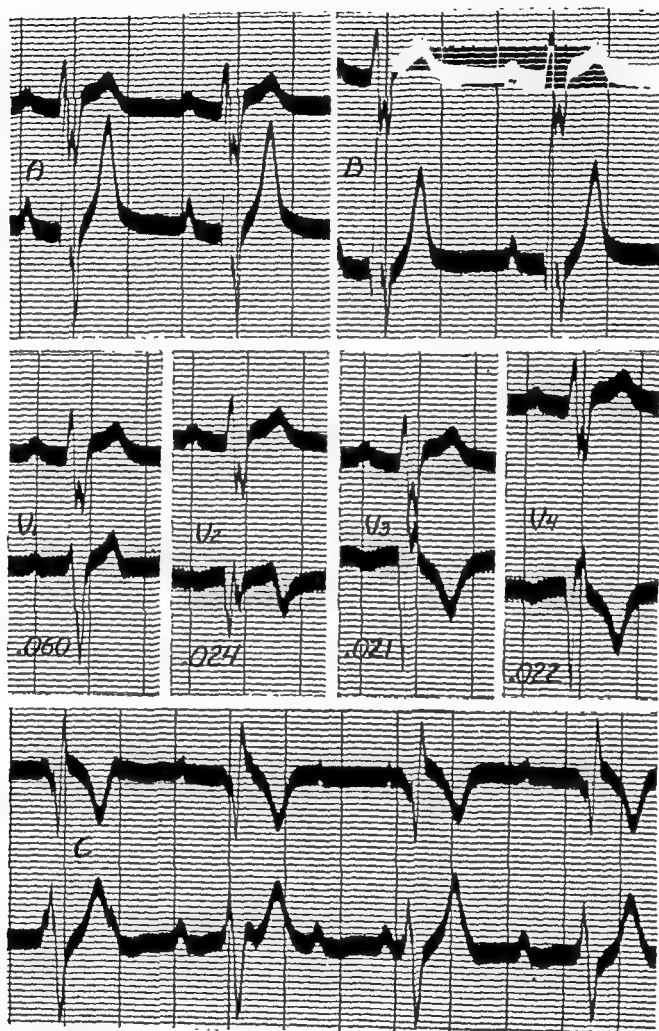


Fig. 2.—Experiment 46. Electrocardiograms taken forty-eight hours after ligation of the septal artery. *A*, Lead I (above) and Lead II; *B*, Lead I and Lead III. The second row shows four precordial leads taken simultaneously with Lead I. In the precordial curves 1 cm. equals 2 millivolts. The indifferent point paired with each exploring electrode was a central terminal (see text). The position of the different exploring electrodes was as follows: V_1 , 6 cm. to the right of the midline; V_2 , in the midline; V_3 , 6.25 cm. to the left of the midline; V_4 , 11.5 cm. to the left of the midline. The figures written on the records give the time (in seconds) of the chief upstroke with reference to the beginning of the QRS interval. *C*, Lead I and Lead III taken after opening the chest. Complete heart block is present.

experiment previously reported³ in which the right branch of the His bundle was cut.

After the precordial leads had been taken, the chest was opened; but before the heart could be exposed, complete atrioventricular block developed. It persisted to the end of the experiment, and direct curves

which could be compared with those taken from the precordium were not therefore obtained. The idioventricular complexes were extremely variable in form, and although direct leads were taken it was not possible to determine with certainty where the ventricular center or centers responsible for the various types of complexes were located. When the ventricular complexes were of the kind shown in Fig. 2, it was thought that the ventricular rhythm arose on the left side. A sharp electrode, insulated except at the tip, failed to yield deflections of the monophasic type when it was thrust through the wall of the right ventricle into the septal muscle, indicating that this muscle, or much of it, was dead.

A photograph of the left side of the septum showing the location of the infarct is shown in Fig. 3. The right side of the septum showed



Fig. 3.—Experiment 46. Photograph of the endocardial surface of the left ventricle.

extensive changes of a similar kind, affecting its upper two-thirds. When the septum was sectioned, a large cavity due to liquefaction necrosis was found extending about 1.5 cm. downward from the upper margin. On microscopic examination this cavity was seen to be surrounded by a zone of dense leucocytic infiltration in necrotic muscle. Outside this zone there was an extensive area of patchy necrosis.

In the other instance (Experiment 51) in which the septal artery was ligated, the standard leads showed complete right branch block with ventricular complexes not strikingly different from those usually obtained after the right branch of the His bundle has been cut (Fig. 4). The form of these complexes was considerably altered by opening the chest, but remained the same in general outline. The precordial curves are somewhat distorted by alternating current. The exploring electrodes were sewn beneath the skin along a line which crossed the precordium

in a base-apex direction and intersected the midline at an angle of about seventy-eight degrees 17 cm. below the episternal notch. In the curve taken farthest to the right the chief upstroke of QRS begins about 0.04 second after the beginning of the QRS interval. In that taken furthest to the left the chief upstroke of QRS occurs about 0.02 second after the beginning of the QRS interval. In form the precordial

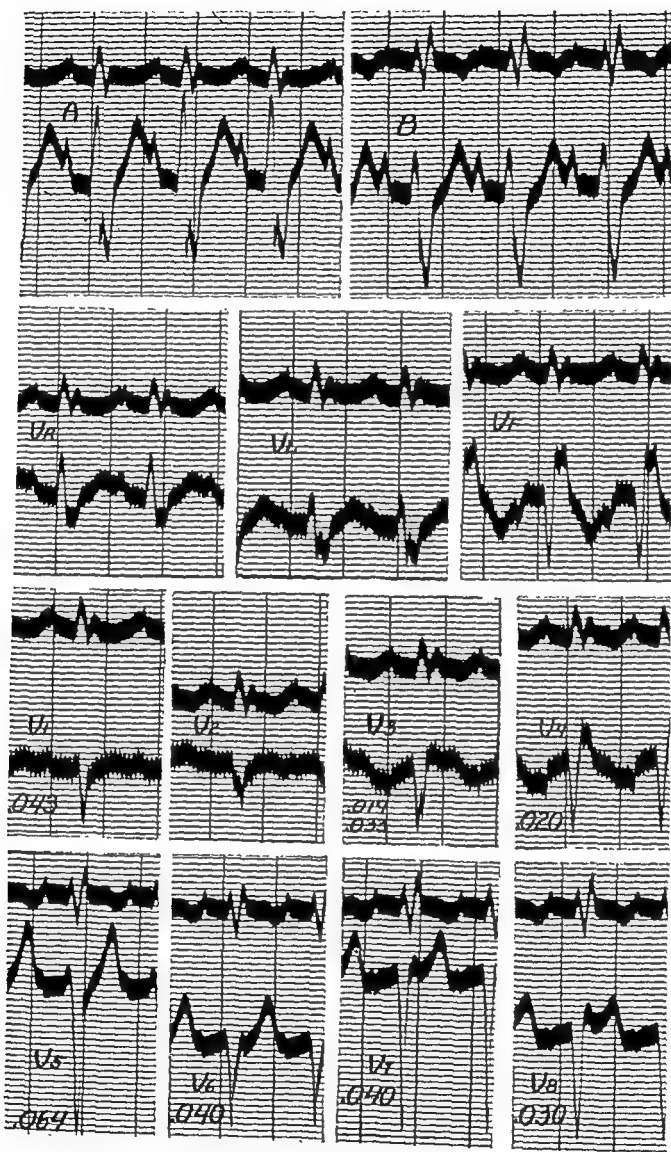


Fig. 4.—Experiment 51. Electrocardiograms taken forty-eight hours after ligation of the septal artery. A, Lead I (above) and Lead III before, and B, the same leads after opening the chest. V_R , the potential of the right fore leg. V_L , the potential of the left fore leg. V_F , the potential of the left hind leg. Third row shows four precordial curves taken simultaneously with Lead I by the same method as the corresponding curves of Fig. 2 except that here 1 cm. equals 1 millivolt. The position of the various exploring electrodes was as follows: V_1 , 6.5 cm. to the right of the midline; V_2 , in the midline; V_3 , 9.5 cm. to the left of the midline. The position of the last row shows a series of leads taken from a gauze pad soaked in saline and laid upon the exposed heart. In these curves 1.5 cm. equals 10 millivolts. The exploring electrode was moved 1.5 to 2 cm. per step in a base-apex direction. V_5 was taken from that part of the pad that lay on the base of the right ventricle and V_6 from that part that lay on the apex of the left ventricle. The time of the chief upstroke with reference to the beginning of the QRS intervals is written on the records in ink.

curves are similar to the corresponding curves of the previous experiment. The indifferent point was again a central terminal connected to the two fore legs and the left hind leg through resistances of 5,000 ohms. Leads from the first three precordial electrodes were, however, also taken by placing the indifferent electrode on the left hind leg. Usually the precordial curves taken by the two methods show only minor differences, but in this instance the curves taken by the second method are very different from those obtained by the first and are so strikingly alike in form that it is clear that they are dominated by the potential of the hind leg electrode (Fig. 5). The potential variations of this electrode and of the electrodes on the two fore legs were recorded by the method described in a preceding article.² The curve from the left hind leg is very much like those from the left side of the precordium (Fig. 4).

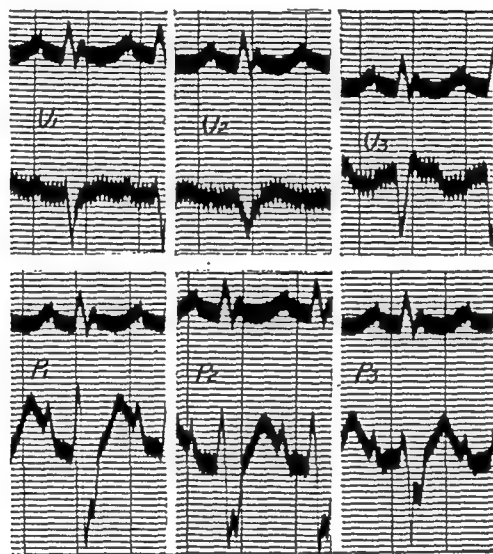


Fig. 5.—Experiment 51. The upper records are the same as V_1 , V_2 and V_3 of Fig. 4. The lower records were taken from the same exploring electrodes, but these were paired with the left hind leg electrode instead of with the central terminal.

The curves from the two fore legs are very much alike and are somewhat similar to those from the right side of the precordium (Fig. 4). Semi-direct leads from a pad soaked in saline and laid upon the exposed heart were also taken, using the central terminal as the indifferent point. As in the case of the precordial leads, the curve taken farthest to the right shows a late, and that taken farthest to the left an early, chief upstroke. The pad curves and the corresponding precordial curves are similar in general outline (Fig. 4).

Before direct leads could be taken, the heart dilated and the animal died. Photographs of the right and left sides of the septum are reproduced in Fig. 6. On the left side the apex of the anterior papillary muscle was infarcted; this part of the lesion is apparently due to the

unintentional obstruction of a small artery on the left margin of the heart at the time of the ligation operation. Practically the whole of the upper septum was necrotic; on microscopic examination there was a small area of autolytic softening surrounded by a heavy zone of leucocytic infiltration.



Fig. 6.—Experiment 51. Photographs of the endocardial surface of the left and right ventricles.

In a fourth experiment (Experiment 48) a septal infarct was produced accidentally. A large division of the septal artery lies just beneath the endocardium on the right side of the septum. In attempting unsuccessfully to cut the right branch of the His bundle this artery was severed. Electrocardiograms taken one week later were not strik-

ingly abnormal. They showed moderate left axis deviation with a prominent R spike in Leads I and II and large S deflections in Leads II and III. The infarct was not discovered until the heart was opened. It was visible only on the left side of the septum and was circular and about 3 cm. in diameter. The posterior subdivision of the left bundle branch crossed the region involved; the anterior subdivision did not.

COMMENTS

The experiments described are of interest from several points of view. The first (Experiment J) shows that the ligation of a coronary artery is followed by displacement of the RS-T segment of the ventricular complex even when the affected muscle lies in the septum and the epicardial surface of the heart is not involved. The last two experiments indicate that precordial leads may be of great value in locating the conduction defect when the ventricular complexes of the standard leads are of unusual outline. In bundle-branch block the precordial curves are often characteristic in every respect when the standard curves are not. The third experiment shows also that when the potential variations of the precordium are unusually small, the method of taking precordial leads in which a central terminal connected to the apices of the triangle formed by the three standard leads is used as the indifferent point has great advantages over that in which the indifferent electrode is placed on one of the extremities.

In the bovine heart, strands of Purkinje tissue which pass through the septum and join the Purkinje network of the right to that of the left ventricle have been described by Wahlin⁴ and by Cardwell and Abramson.⁵ Rothberger⁶ has advanced the view that similar tracts of special tissue cross the septum in the dog's heart. If we understand him correctly, he believes that the destruction of these tracts should considerably increase the QRS interval of branch-block curves. Referring to Mahaim's views⁷ with respect to the lesions responsible for the electrocardiographic changes attributed to arborization block, he suggests that widespread lesions of the septum which destroy the connections between the Purkinje systems of the two ventricles and also involve the bundle branches to a greater or less extent should produce curves of this kind. So far as our experiments have any bearing upon these opinions, they do not tend to confirm them. The QRS interval is apparently no greater in right branch block when it is produced by septal ligation than when it is produced by cutting the right branch of the His bundle. The ventricular complexes do not resemble those attributed to arborization block more in the one case than in the other. If connections between the terminals of the two bundle branches were present in our animals, it is of course possible that they escaped destruction either be-

cause they lay outside the infarcted region or because Purkinje tissue is less easily killed by cutting off its blood supply than is ordinary heart muscle. It is evident that some of the subdivisions of the left bundle branch which crossed the infarcted area continued to conduct. Lack of suitable equipment made it impossible to make serial sections of the infarcted region.

ORIGIN OF THE PRELIMINARY DEFLECTIONS OF THE LEVOCARDIOGRAM

The experiments under consideration and some observations made in experiments of the same series in which other coronary vessels were ligated are of interest from still another standpoint. In right branch block the deflections inscribed during the first part of the QRS interval represent the spread of the excitatory process over the muscle of the left ventricle. Each part of this muscle as it becomes active plays its individual part in the formation of these deflections. When a section of the septal or of the free wall of the left ventricle is dead, the electrical forces that it normally produces can no longer occur. A study of the ventricular complexes of dogs with right branch block and extensive infarcts of the left ventricular wall should therefore give some indication of the origin of the various deflections of the normal canine levocardiogram. In the case of septal infarcts all the subdivisions of the left branch of the His bundle cross the infarcted region. It cannot be assumed that these tracts always escape injury and that all the changes in the levocardiogram produced by ligation of the septal artery are due solely to destruction of the part of the left ventricular wall affected. Injury to the specialized tissues probably plays no important rôle in determining the alterations in the levocardiogram produced by infarcts of the free wall.

It should be pointed out also that the electrocardiographic changes that occur during the earlier stages of infarction are not due to death of the affected muscle. The immediate effects of coronary ligation are the result of injury to the cell membranes of the muscle fibers whose blood supply has been cut off; ten or twelve hours must elapse before the fatally injured tissues become incapable of producing potential differences. It may take even longer for the injury currents set up at the margins of the infarct to subside completely. We shall therefore consider only those electrocardiograms that were taken at least twenty-four hours after a coronary artery was ligated. The form of the canine levocardiogram varies considerably from animal to animal. Minor changes in this curve cannot be detected unless control curves from the same animal are available for comparison. Since such material is not at our disposal, we must be satisfied for the present with such information as may be obtained by comparing the right branch-block curves of dogs with extensive infarcts and those of healthy animals.

Some years ago Lewis⁸ made a careful study of the ventricular complexes that characterize right branch block in the dog under conditions similar to those that obtained in our experiments. He found that the great majority of animals give concordant curves in which the chief initial deflection (S) is downward in all three leads. In his experiments its value in Lead I usually lay between 0.2 and 1.3 millivolts; in Lead III, between 1.1 and 2.5 millivolts. The preliminary deflections ordinarily consisted in a small downward movement (Q) followed by an upward excursion (R). The value of the former varied between 0 and 0.2 millivolt in Lead I and between 0 and 0.15 millivolt in Lead III; that of the latter between 0.1 and 0.3 millivolt in Lead I and between 0.2 and 0.9 millivolt in Lead III. In a few animals the levocardiogram was discordant, and the chief initial deflection of Lead I was upward. Lewis gave measurements of the curves obtained in twelve experiments; in half of these right branch block was produced by means of a clamp, and the possibility that some of the anterior subdivisions of the left bundle branch were damaged cannot be excluded. Similar measurements of the right branch block curves of twenty-two animals are shown in Table I (H2 to H18 inclusive). To conserve space, measurements of Lead II are omitted. Most of these curves were taken by Wilson and Herrman⁹ in the course of their work on incomplete bundle-branch block. In all the experiments the animal was placed on its back and the chest was opened by splitting the sternum. In the last ten (H6 to H18 inclusive) one or more attempts to cut the left branch of the bundle were made before the right branch was attacked. In four (H7, H16, H17 and H22) of these ten experiments the cuts on the left side produced transient left branch block, but the ventricular complex regained its normal form before the right branch block was produced. No experiment is included in which the major subdivisions of the left branch were not intact when the heart was opened. With a few minor exceptions all the measurements fall within the limits given by Lewis. Table I also gives measurements of the right branch block curves of ten dogs with infarcts of various kinds (Experiments 46 et seq.). The curves are reproduced in Figs. 2 B, 4 B, and 7 B, D, F, H, K, M, O and Q.

The levocardiogram of the first animal (Experiment J) in which the septal artery was tied is of the discordant type, but all the deflections of Lead I are small. Since we cannot assume that the infarcted muscle was dead when the electrocardiograms were taken, this experiment is not suitable for our present purpose. The ventricular complexes of the second animal (Experiment 46) are of unusual outline, particularly in Leads II and III. In the latter lead, Q is abnormally deep and R is greatly exaggerated. The final downward movement (S) is less pro-

TABLE I

EXP. NO.	BICARDIOGRAM			LEAD III			QRS INT.			LEVOCARDIOGRAM			LEAD III		
	LEAD I			LEAD I			SECONDS			LEAD I			LEAD I		
	Q R S			Q R S			Q R S			Q R S			Q R S		
	Q	R	S	Q	R	S	Q	R	S	Q	R	S	Q	R	S
H2	2.0	6.0	0.0	0.0	6.0	1.0	0.083	0.083	1.0	0.5	5.5	5.0	T	1.5	5.0
H3	0.0	5.0	0.0	T	18.0	1.0	0.075	0.075	0.0	1.5	4.0	8.0	0.5	7.0	8.0
H21	0.0	7.0	1.0	0.0	21.0	4.0	0.075	0.075	0.0	1.5	8.5	10.0	0.5	9.0	10.0
H26	0.0	3.5	0.0	1.0	20.0	9.0	0.074	0.074	0.0	3.0	5.0*	17.0	1.0	5.0	17.0
H28	0.0	6.0	0.5	0.0	14.0	8.0	0.091	0.091	0.0	5.5	4.0*	10.5	0.0	6.0	10.5
H29	0.0	8.0	T	0.5	12.0	1.0	0.078	0.078	0.0	4.0	6.0	8.5	0.0	9.0	8.5
H30	0.0	10.0	0.0	0.0	4.0	3.0	0.084	0.084	0.0	3.0	2.0*	10.5	0.0	1.0	10.5
H32	0.0	5.0	1.0	0.5	9.0	0.5	0.096	0.096	0.0	3.5	5.0*	12.0	0.5	3.5	12.0
M62	1.0	6.0	0.0	1.0	25.0	0.0	0.079	0.079	0.0	2.0	4.0	3.0	0.5	5.0	3.0
M60	1.0	8.0	0.0	1.0	17.0	1.0	0.068	0.068	1.0	1.5	10.0	12.0	T	11.5	12.0
H1	-	-	-	-	-	-	0.077	0.077	T	T	6.0	10.0	T	0.5	10.0
M56	-	-	-	-	-	-	0.076	0.076	0.5	1.0	6.0	16.0	0.0	13.0	16.0
H6	0.0	2.0	0.0	0.0	9.0	1.0	0.080	0.080	0.5	T	8.0	10.0	T	4.0	10.0
H7	1.0	7.5	0.0	0.0	5.0	4.5	0.086	0.086	0.5	1.0	0.5	10.5	0.0	1.5	10.5
H10	T	5.5	0.0	0.0	10.5	6.0	0.089	0.089	T	2.0	3.0	12.0	0.5	3.0	12.0
H12	1.0	5.0	0.0	0.5	15.0	0.0	0.083	0.083	1.0	0.5	9.5	8.0	0.5	5.0	8.0
H15	0.5	7.0	0.0	T	19.0	4.0	0.084	0.084	1.5	3.0	8.0	25.0	T	11.0	25.0
H16	1.0	5.5	0.0	0.0	13.0	7.0	0.072	0.072	1.0	1.5	6.0	16.0	0.0	5.5	16.0
H17	T	6.0	0.0	0.0	14.0	4.0	0.076	0.076	0.5	1.5	3.0	15.0	0.0	3.5	15.0
H22	1.0	5.0	0.0	0.0	16.5	3.5	0.070	0.070	0.0	0.5	7.0	15.0	0.0	1.0	15.0
H24	1.0	4.0	0.0	0.5	23.0	1.0	0.074	0.074	0.5	1.0	8.0	14.5	T	13.0	14.5
H18	-	-	-	-	-	-	0.089	0.089	0.0	0.0	7.0	10.0	0.0	6.0	10.0
46	-	-	-	-	-	-	0.080	0.080	0.0	6.5	7.5	8.5	3.0	26.0	8.5
51	-	-	-	-	-	-	0.083	0.083	0.0	2.5	3.0*	14.0	0.0	5.5	14.0
11	0.053	4.0	T	T	6.5	0.0	0.073	0.073	0.0	1.5	8.0	8.5	0.5	1.0	8.5
15	0.049	3.0	1.0	0.0	6.5	0.0	0.080	0.080	T	0.0	10.5	7.0	0.0	3.5	7.0
19	0.057	6.0	1.0	0.0	6.0	T	0.087	0.087	0.0	0.0	10.5	7.5	0.0	5.0	7.5
14	0.056	6.0	2.5	0.0	3.5	5.5	0.090	0.090	0.0	0.0	10.0	8.5	0.0	3.0	8.5
29	0.055	10.0	1.0	0.0	3.0	10.0	0.075	0.075	0.0	0.0	8.0	6.0	0.0	0.0	6.0
41	0.061	1.0	0.0	7.5	0.0	0.0	0.086	0.086	0.0	0.0	3.5	10.0	0.0	0.0	10.0
42	0.055	0.0	0.0	0.5	20.0	1.5	0.082	0.082	0.0	2.5	8.5	14.0	1.5	2.5	14.0
38	0.048	0.0	0.0	0.0	6.5	2.0	0.085	0.085	0.0	T	10.0	7.5	0.0	2.0	7.5

*In these instances S was followed by a conspicuous summit.
Measurements given in tenths of a millivolt. "T" equals trace.

nounced than usual. The onset of complete atrioventricular block with idioventricular complexes of varying form suggests that the left bundle branch was seriously damaged and eventually failed completely. It is possible that only a single subdivision was functioning when the first curves were taken. Ventricular complexes strikingly similar in form were obtained by Rothberger and Winterberg¹⁰ (their Plate X, Figs. 8e and 8f) in an experiment in which they had cut the right and all the more posterior subdivisions of the left bundle branch. Complexes in which the chief initial deflection is upward in Lead III appear to be frequent under these circumstances. Such curves (Fig. 8 *H*) were obtained in one of our experiments in which the incisions on the right side of the septum were so deep that they reached almost through it. When the heart was opened an extensive extravasation of blood was found about the posterior branches of the left division. It seems probable that the peculiarities of the ventricular complexes in our second septal experiment were due mainly to blocking of these tracts. It is of course uncertain what effect opening the chest might have had upon the form of these curves.

In the third experiment (Experiment 51) the form of the branch block complexes is less unusual. They are not clearly outside normal limits. In view of the large amount of muscle infarcted this is somewhat of a surprise. It is probable, however, that if control curves from the same animal were available for comparison, definite changes could be detected.

The electrocardiograms taken before and after cutting the right branch of the His bundle in five experiments in which the anterior descending branch of the left coronary artery had been ligated at least twenty-four hours before are reproduced in Fig. 7. The bicardiograms are similar to the human curves obtained in coronary thrombosis affecting the same vessel.¹¹ In Lead I the first ventricular deflection (*Q*) is downward and is of large amplitude; in Lead III the first deflection is upward. The right branch block complexes of the first set of curves (Experiment 11) are not abnormal. The ligation operation was performed seventy-eight days before the electrocardiographic studies were made. There was an extensive subendocardial sclerosis on the ventral wall of the left ventricle; this lesion penetrated the wall over an area a centimeter or less in diameter. When the right side of the heart was opened, no cut crossing the course of the right division could be seen, but it is evident that this bundle must have been damaged. The second set of curves (Fig. 7 *C* and *D*) is from an experiment in which the infarct penetrated a narrow strip of the left ventricular wall on the left margin of the heart. The lesion was more extensive on the endocardial surface and involved the anterior papillary muscle. In three experiments (14, 19, and 29) the infarct was very large and involved the greater part of

the ventral and left lateral wall of the left ventricle, and the adjacent portions of the ventral wall of the right ventricle. In the branch block complexes of the last four experiments (15, 19, 14, and 29) the preliminary deflections (Q and R) of Lead I either are absent or are represented merely by an irregularity on the descending limb of the chief deflection (S), which is unusually deep. In the last experiment the preliminary deflections are absent in Lead III as well (Fig. 7-K). In this instance the apex and the apical third of the dorsal wall of the left

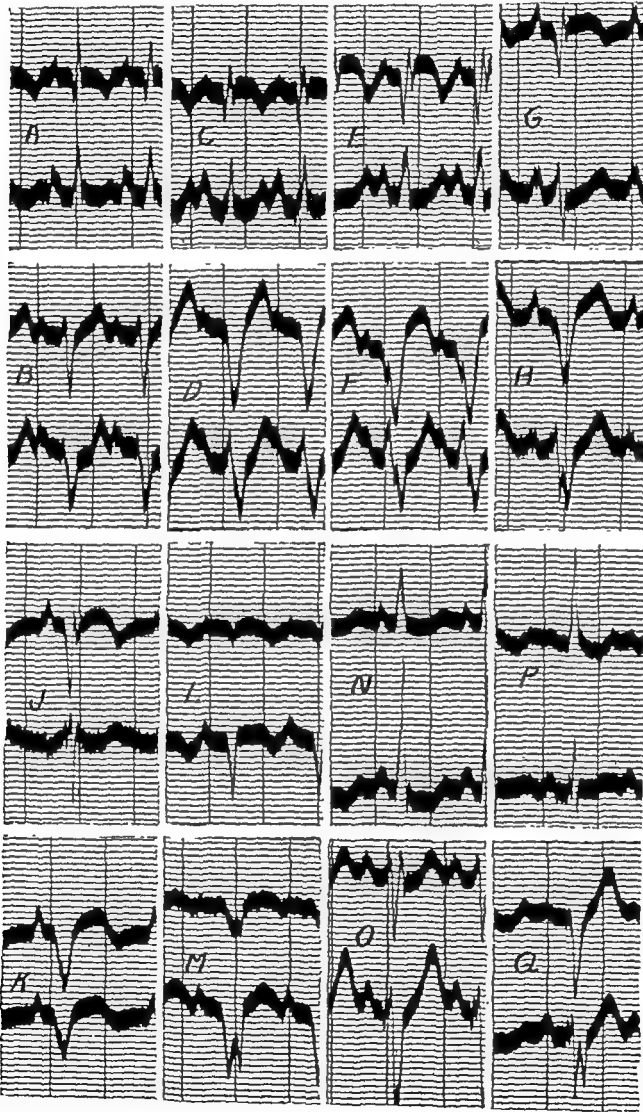


Fig. 7.—The bicardiograms (Leads I and III) and right branch-block complexes (same leads) of a series of dogs with myocardial infarcts. *A* and *B* are from Experiment 11, and were taken seventy-eight days after ligation of the anterior descending branch of the left coronary artery. *C* and *D* are from Experiment 15, and were taken twenty-four hours after ligation of the anterior descending artery. *E* and *F* are from Experiment 19 and were taken forty-eight hours after ligation of the anterior descending artery. *G* and *H* are from Experiment 14 and were taken forty-eight hours after ligation of the anterior descending artery. *J* and *K* are from Experiment 29 and were taken ninety-six hours after ligation of the anterior descending artery. *L* and *M* are from Experiment 41 and were taken forty-eight hours after ligation of the circumflex branch of the left coronary artery. *N* and *O* are from Experiment 42 and were taken forty-eight hours after ligation of the right coronary artery. *P* and *Q* are from Experiment 38 and were taken five days after ligation of the right coronary artery.

ventricle, as well as practically the whole of the ventral wall, were included in the infarct.

While it is true that either or both of the preliminary deflections of Lead I may be inconspicuous in the right branch block complexes of normal animals (see Table I), this is distinctly unusual, and the probability that it would occur accidentally in four experiments in succession is very small. We attribute the peculiarities of both the levocardiogram and the bicardiogram in these experiments to the absence of the electrical effects normally produced by the spread of the excitatory process over the infarcted region.

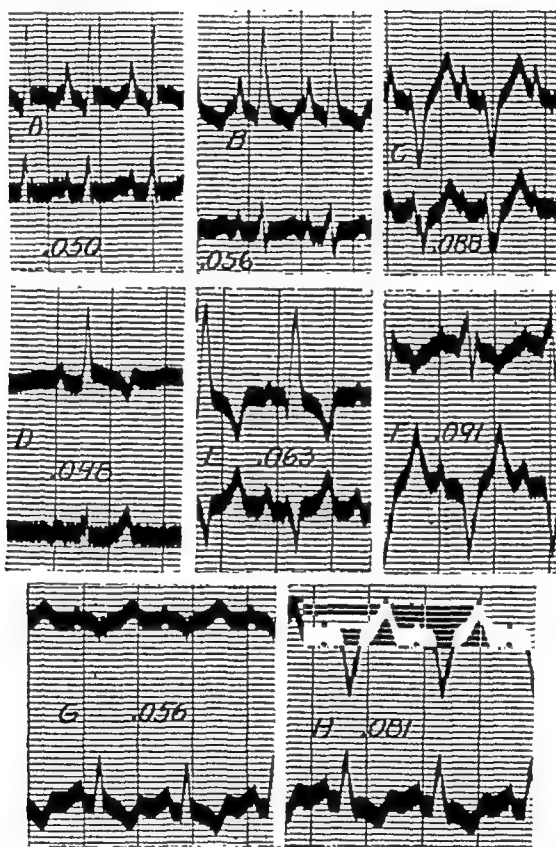


Fig. 8.—All records show Lead I and Lead III taken simultaneously. Figures written on the records give the QRS interval in seconds. Top row: Experiment 45. *A*, after opening the chest; *B*, after cutting the anterior subdivisions of the left bundle branch; *C*, after cutting the right bundle branch. Middle row: Experiment 50. *D*, after opening the chest; *E*, after cutting the anterior subdivisions of the left bundle branch; *F*, after cutting the right bundle branch. Bottom row: Experiment 13. *G*, after opening the chest. *H*, after cutting right bundle branch. There was pronounced extravasation of blood about the posterior subdivisions of the left bundle branch.

It should be pointed out that these changes are not due to damage to the anterior subdivisions of the left bundle branch, which transmit the excitation wave to the region affected. The electrocardiograms taken in two experiments in which these tracts were cut are reproduced in Fig. 8. It will be observed that the changes in the bicardiogram produced by this procedure are quite different from those observed follow-

ing ligation of the anterior descending coronary artery. The latter cannot therefore logically be attributed to intraventricular block affecting the tracts in question. Except for the absence of distinct preliminary deflections in Lead III in one set of curves (Fig. 8-*F'*) the branch block complexes of these experiments are not unusual. The levocardiograms are not of the discordant type in which the chief deflection of Lead I is upward, as is often the case when the anterior branches of the left division have been injured.^{10, 9} Ligation operations, partly unsuccessful,* had been performed on both of the animals used in these experiments. In each case a small infarct involving only the inner layers of muscle, and approximately a centimeter in diameter, was discovered when the left ventricle was opened. In one instance the lesion involved the base of the anterior papillary muscle; in the other it lay just above the apex of this structure. It seems unlikely that these infarcts had any important influence on the form of the ventricular complexes.

The sixth set of curves (L and M) shown in Fig. 7 is from an experiment in which the circumflex branch of the left coronary artery was ligated forty-eight hours before the electrocardiograms were taken. In Lead I the ventricular deflections of the bicardiogram are very small; in Lead III the first and chief deflection (Q) is downward. Similar changes in the bicardiogram in Lead III are seen in coronary thrombosis in man, when the infarct is on the posterior wall of the heart.¹¹ In the branch block curves preliminary deflections are absent both in Lead I and in Lead III. The last two sets of curves are from animals with infarcts of the right ventricle produced by ligation of the right coronary artery. In the bicardiograms the first ventricular deflection is upward in both Lead I and Lead III. In one instance the preliminary deflections of the levocardiogram are inconspicuous in Lead I, but the branch block curves are not strikingly peculiar in other respects.

While the experiments described do not enable us to identify with certainty the portions of the left ventricular muscle chiefly responsible for the various deflections of the canine levocardiogram, they offer a few valuable suggestions. Since the larger of the preliminary deflections (R) is preserved when a large part of the septum proper is destroyed, but tends to disappear when the free wall is extensively involved, it is hardly possible that this deflection can be of septal origin. The changes in the bicardiogram produced by infarcts that involve the ventral and those that involve the dorsal wall, respectively, would lead us to expect that this peak would be abolished in Lead I by infarcts of the former, and in Lead III by infarcts of the latter kind. This is essentially what we find to be the case. The infarcts produced by ligation of the anterior descending artery usually involve the left margin of the heart, and it is

*The large vessel selected for ligation was missed.

probably the activation of this portion of the wall that contributes most to R of the levocardiogram in Lead I. These infarcts also tend to involve the muscle to which the anterior margin of the septum is attached, but do not in the dog extend to the septum proper. The infarcts produced by occlusion of the posterior descending artery* usually face toward the left leg in man and toward the left hind leg in the dog. These parts of the wall when uninfarcted produce electrical effects that tend to make this extremity relatively positive, and are chiefly responsible for R of the levocardiogram in Lead III. Infarction of these parts, by subtraction of these electrical effects causes disappearance of the R deflection, and its replacement by a downward deflection in that lead. These infarcts also tend to involve the muscle to which the posterior margin of the septum is attached. We believe that the infarction of those portions of the wall attached to the septal margins is unimportant so far as the disappearance of the preliminary deflections of the levocardiogram is concerned† both in the case of ventral and in the case of dorsal infarcts. This muscle must be activated in the same general direction as the septum proper and should produce similar electrical effects.

The other preliminary deflection (Q) is inconstant in healthy animals, and its identification depends upon the presence of an R summit. Consequently, our observations throw very little light upon its origin. We may point out that a large Q deflection may be present in Lead III when a large part of the septum is dead (Fig. 2). It seems probable nevertheless that in normal animals Q of the levocardiogram is produced by muscle on the septal rather than by muscle on the left lateral side of the left ventricle. One should not be confused by a terminology that is convenient for the purposes of description, but has nothing to do with origins. The current terminology, which we do not propose to change, refers to Q as any initial downward deflection preceding the upstroke R; it is not concerned with the origin of this deflection. The small deflection under consideration is not analogous to the Q deflection of the human levocardiogram except in cases where the human levocardium is similar to that of the dog. When in branch block curves the chief and broadest QRS deflection in one lead is upward, the small depression that precedes it, though technically called Q, is really in causation analogous to a preliminary R deflection upside down.

In a previous article the view was advanced that the chief initial deflection of the levocardiogram (S) is not due to activation of the free

*In the dog this vessel is derived from the circumflex branch of the left coronary; in man it is usually derived from the right coronary.

†The form of the bicardiogram after ligation of the anterior descending or of the circumflex branch of the left coronary suggests that this procedure alters the form of the dextrocardiogram as well as that of the levocardiogram. After ligation of the former vessel stimulation of the anterior surface of the right ventricle may yield in Lead I complexes that begin with a deep downward excursion.

wall of the left ventricle, but is of septal origin. This statement referred, of course, to the descending limb of the large downward deflection in right branch block, and not to the later portions of this deflection which are clearly contributed by right ventricular muscle. One might therefore expect infarcts of the lateral wall to increase, and infarcts of the septum to decrease the size of this deflection. The matter is, however, somewhat complicated. First of all, we do not usually know in an individual case of right branch block at exactly what point right ventricular effects begin to modify the true levocardiogram. In the second place, infarcts of the lateral wall cannot modify deflections normally written by the septum after the activation of the lateral walls has been completed; septal infarcts cannot modify deflections ordinarily written by the right ventricle after activation of the septum has been completed. If the right ventricular effects are alone responsible for the deepest part of S, infarction of the septum can do no more than alter the position and slope of the descending limb of this deflection. Theoretically, infarcts of the septum and infarcts of the lateral wall of the right ventricle should, however, if the view under consideration is correct, algebraically diminish the area of the initial deflections in right branch block. Infarcts of the lateral wall of the left ventricle, on the other hand, should increase this area. The observations reported here do not either confirm or discredit the hypothesis that the chief deflection of the levocardiogram is of septal origin. The changes in S, if present, are not pronounced enough to enable us to detect them without control observations on the same animals made before the infarcts were produced. In the absence of control curves it has seemed useless to measure the areas of the initial deflections, a laborious operation. It may be noted that in the experiments in which the anterior descending artery was ligated S does appear to be unusually deep and the area of the initial deflections unusually small (absolutely large but negative in sign) in Lead I. In one of the septal experiments S is small and the area positive in the same lead. In Lead III, however, S is deeper and the area more negative in the latter experiment than in any of the former group. Since any conclusions must involve assumptions difficult to justify, it is not worth while to discuss this matter further at this time.

Since infarcts of the free wall modify R of the levocardiogram, at least part of the muscle affected must normally begin to produce potential differences very early in the QRS interval. We strongly suspect that practically all the endocardial surface of the left ventricle is already active when the upstroke of this deflection begins. Apparently the muscle that contributes to even the earliest ventricular deflections in standard leads is very widely distributed. For this reason it is difficult

to determine the origin of any of the QRS deflections in terms of the muscle region or regions responsible for them. Attempts to do so have often led to misconceptions.

One difficulty in the solution of this problem lies in the fact that the QRS group has no natural divisions. The first deflection, for example, varies from lead to lead in size, in direction and in duration. The muscle responsible for this deflection not only varies with the lead, but in any given lead is not necessarily the same in animals of different species nor even in different individuals of the same species.

SUMMARY

Ligation of the septal branch of the left coronary artery in the dog is usually followed by infarction of a large part of the ventricular septum. Immediately after this vessel is obstructed the electrocardiogram shows displacement of the RS-T segment of the ventricular complex. Later, disturbances of intraventricular or atrioventricular conduction develop; right bundle-branch block occurred in all three of our experiments. In one instance the right branch block complexes were not strikingly different from those usually obtained after the right branch of the His bundle has been cut, in spite of the fact that a large part of the septal muscle was dead.

In right bundle-branch block the precordial electrocardiograms may be characteristic in every respect when the standard electrocardiograms are not. Under these circumstances precordial leads are of great value in locating the conduction defect. When the potential variations of the precordium are small, the precordial electrodes should not be paired with a single electrode, but with a central terminal connected through like resistances of 5000 ohms or more to all three extremity electrodes.

The R deflection of the levocardiogram is not abolished by infarction of the septum but is frequently absent in Lead I after ligation of the anterior descending and in Lead III after the ligation of the circumflex branch of the left coronary. This deflection is not of septal origin. The muscle responsible for the preliminary deflections of the levocardiogram is widely distributed, and it is probable that most of the endocardial surface of the left ventricle is active before the first summit of the levocardiogram is written.

NOTE: We wish to thank Prof. C. V. Weller and the members of his staff for making and examining microscopic sections of the infarcts produced in our experiments.

REFERENCES

1. Lauterbach: *Ztschr. f. d. ges. exper. Med.* 41: 665, 1928.
2. Wilson, Johnston, Macleod, and Barker: *AM. HEART J.* 9: 447, 1934.
3. Wilson, Johnston, Hill, Macleod, and Barker: *AM. HEART J.* 9: 459, 1934.
4. Wahlin: *Uppsala läkaref. förh.* N. F. 34: 769, 1928.
5. Cardwell and Abramson: *Am. J. Anat.* 49: 167, 1931.

6. Rothberger: *Ztschr. f. d. ges. exper. Med.* 87: 763, 1933.
7. Mahaim: *Ann. de Med.* 32: 347, 1932.
8. Lewis: *Phil. Trans. Roy. Soc. (London) Series B.* 207: 221, 1916.
9. Wilson and Herrman: *Heart* 8: 229, 1921.
10. Rothberger and Winterberg: *Ztschr. f. d. ges. exper. Med.* 5: 264, 1917.
11. Wilson, Macleod, Barker, Johnston and Klostermeyer: *Heart* 16: 155, 1933.

THE INITIAL COMPLEX OF THE ELECTROCARDIOGRAM AFTER INFARCTION OF THE HUMAN HEART*

MAX WINTERITZ, M.D.
PRAGUE, CZECHOSLOVAKIA

FOLLOWING the studies of Herrick,¹ Smith,² and Pardee³ the changes in the final complex (T-wave) and in the S-T interval in cases of coronary sclerosis and thrombosis have been a fertile subject for clinical and experimental research. In contrast, the changes in the initial complex have, up to the present, received little attention. And yet from the first it must seem unlikely that the destruction, often so extensive, of part of the great connected mass of heart muscle should not be reflected in the process of activation of the ventricular muscle and in the corresponding electrical curve. Wearn⁴ and after him a number of other writers have called attention to the decrease in the size of the ventricular waves following coronary thrombosis. Wilson⁵ was the first to point out the appearance of a deep Q-wave in Lead III following coronary closure, a finding which has since received considerable attention. Fenichel and Kugell⁶ extended these observations and held that an unusually deep Q in Leads I and II was also significant. Oppenheimer and Rothschild⁷ found that infarction in the region supplied by the anterior descending ramus resulted in the changes described by them as arborization block, and Mahaim⁸ made clear the relation between myocardial infarct and bundle-branch block.

None of the changes mentioned are pathognomonic for cardiac infarction. We may find low voltage, decrease in the size of the waves of the electrocardiogram, in all cases which are associated with severe impairment of cardiac function. We see this with about the same frequency in cases of acute myocardial infarct, in cases of severe infections or intoxications, in cardiac asthma and at the time of death. Moreover low voltage may be quite lacking in cases of arterial hypertension, or it may appear with pericardial effusion. As a sign we can put low voltage in the class with diminished heart sounds.

We may find a deep Q-wave with coronary thrombosis or with uncomplicated sclerosis, with left axis deviation, with scoliosis and also as a variation of the normal electrocardiogram.^{9, 10}

Of more serious significance is the appearance of deep Q-waves in several leads which we occasionally find in chronic coronary occlusion and old infarcts. Freundlich,¹¹ to be sure, heeded this sign only when abnormal changes in the final complex were also present.

*From the First Medical Clinic of the German University in Prague, service of Dr. Rudolf Schmidt.

The question often arises whether there is not special difficulty in interpreting clinically the electrocardiogram, in how far the changes in the initial complex after coronary thrombosis can be attributed to this insult, when, as is usually the case, the form of the electrocardiogram before the insult is unknown. Since the coronary thrombosis is seldom the first or only pathological change in the heart, preexisting anomalies of the electrocardiogram must always be considered. This is particularly true in cases of arborization and bundle-branch block.

In the following discussion I shall report a series of cases which form a distinct group in that definite electrocardiographic changes of the QRS group correspond with definite myomalacia of the heart

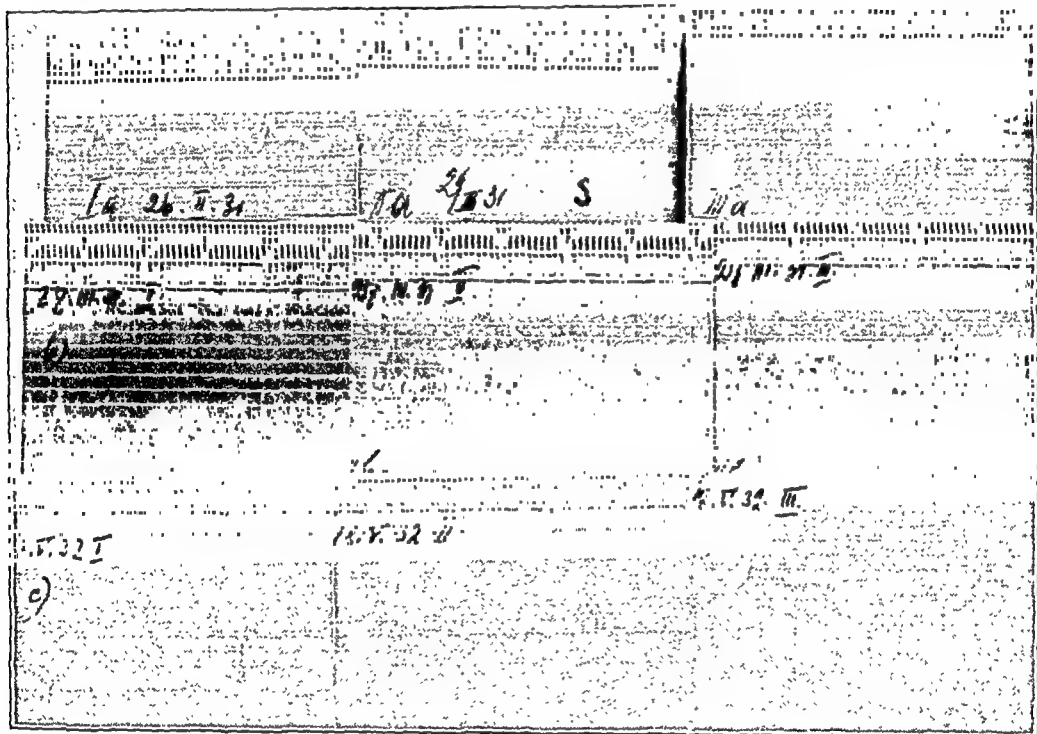


Fig. 1.—Case 1, attack on Feb. 24, 1931.

muscle and make it possible to diagnose myocardial infarct without knowledge of earlier electrocardiograms, of autopsy findings, or even at times of the clinical picture. In addition to our own cases we shall cite cases from the literature in which similar changes were present but not stressed by the authors. First I shall give abstracts of the clinical histories of our patients, mentioning only the essential points and showing only as many of the electrocardiograms as seem necessary.

CASE REPORTS

CASE 1.—Forty-six-year-old letter carrier. Angina on effort since 1926. February 24, 1931, a typical attack with pain referred to the abdomen. Blood pressure on Feb. 26, 116/65 mm., on March 24, 95/65 mm. Recovery after eight weeks. In July, 1932, while taking CO₂ baths he had acute decompensation, and was admitted

to the clinic. Progressive cardiac failure and pulmonary infarction led to death on Aug. 22, 1932. Autopsy:* slight general arteriosclerosis with marked coronary sclerosis and extensive calcification, complete closure of the anterior descending ramus with area of myomalacia 12 cm. in diameter, aneurysm of the ventricular wall large enough to hold a man's fist associated with adherent pericardium, hypertrophy of the left ventricle and great hypertrophy and dilatation of the right ventricle, thrombosis of femoral vein, hemorrhagic pulmonary infarct, chronic passive congestion. Histological examination of the kidneys showed only congestion.

Electrocardiograms. The first electrocardiogram, three days after the insult (Fig. 1a), shows in Lead I the convex T-wave with high take-off from the descending limb of R, while in Leads II and III also T starts above the isoelectric level but lacks the characteristic coronary form, having a form which is not uncom-

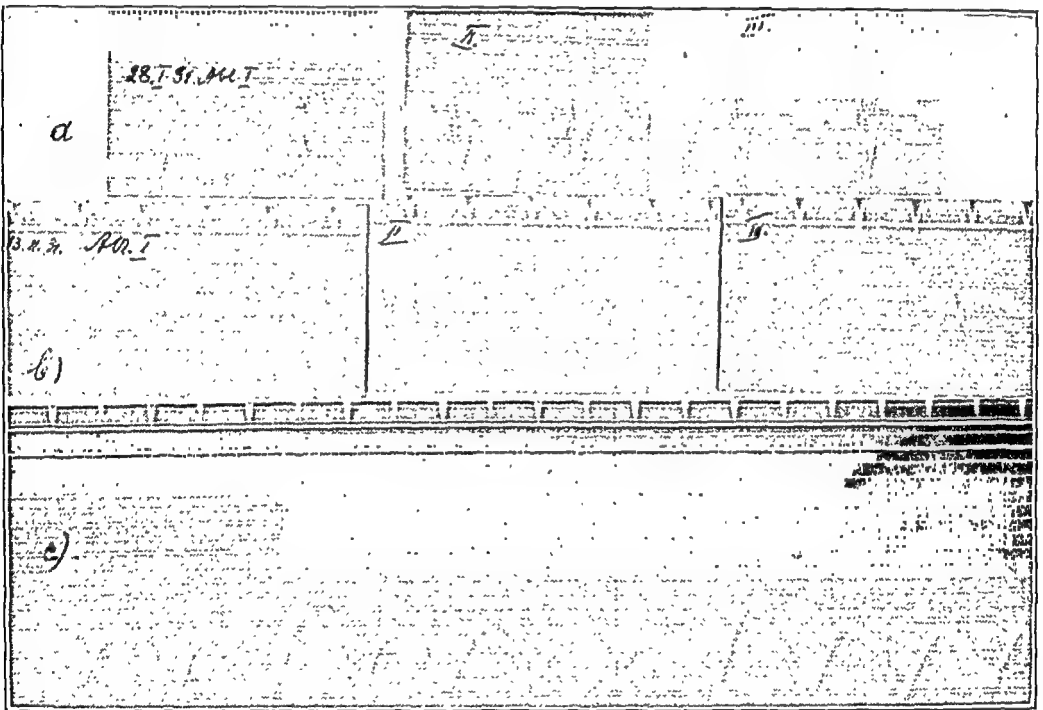


Fig. 2.—Case 2. (a) Twenty-four hours after the attack. (b) seventeen days after the attack, (c) after clinical death.

mon in these leads in cases of left axis deviation. Fig. 1 b and c also illustrates left axis deviation. One also notes the widening of QRS, just missing 0.1 sec. in Lead I and 0.11 sec. in Lead II. Lead I is not typical of left axis deviation in that there is only a rudimentary R following the broad Q-wave. The ratio of R_1 , S_2 and S_3 is 3.5:15:14. After fifteen months we find Q_1 clearly formed and R_1 higher, just missing 9 mm. Left axis deviation, probably present before the insult, has reappeared.

Summary: Thrombosis of the anterior descending ramus with a large infarct and aneurysm in the area supplied by this vessel. In the acute and subacute stages the electrocardiogram showed, together

*All the autopsies reported were performed in the German Pathological Institute, Dr. A. Glon being chief.

with the typical T-wave changes, a left axis deviation but with very small R-waves. After fifteen months the R-waves had become upright.

CASE 2.—Turner, aged fifty-three years. Dyspnea on effort since 1920. January 27, 1931, pain typical of coronary closure, blood pressure at the onset 130/85 mm. On Feb. 17, after several days of tolerable condition, an attack of supraventricular paroxysmal tachycardia with rate of 220 and alarming collapse. As quinine, 0.2 gm. intravenously had no effect, 0.3 gm. was given three hours later. Death followed within a few minutes. Autopsy: advanced sclerosis of the left coronary artery, especially the anterior descending ramus with old thrombosis in its upper third and a resulting aneurysm involving the wall of the left ventricle, the septum and the apex; mural thrombus; thickness of wall of left ventricle in region of venous ostia 15 mm., in region of aneurysm 4 mm.; many smaller scars scattered through the muscle; slight sclerosis of the aorta; congestion and edema of the lungs; kidneys normal except for congestion.

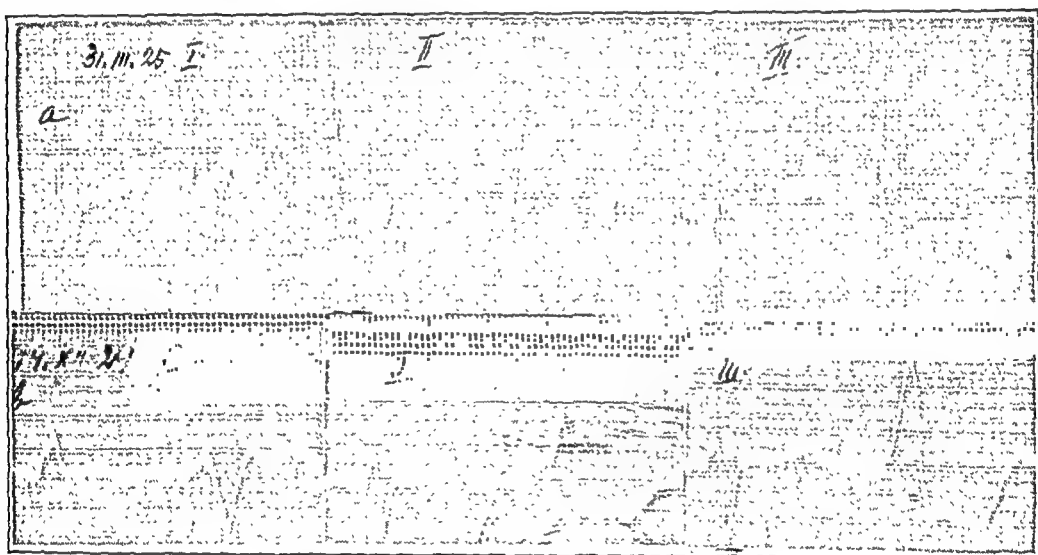


Fig. 3.—Case 3, attack in May, 1929.

Electrocardiograms. Fig. 2a, taken thirty-six hours after the insult, shows in Lead I a low R with typical high take-off and convexity of the R-T segment. Leads II and III show the prominent S of left axis deviation. In the next few days (Fig. 2b) the picture of low voltage appeared in all leads. T shows the characteristic changes. Fig. 2c shows the electrical activity of the dying ventricle.

Summary. Myomalacia with aneurysm of the wall in the area of distribution of the anterior descending ramus following acute coronary thrombosis. In the acute stages the electrocardiogram showed left axis deviation with noteworthy small R_1 and deep S_2 and S_3 .

CASE 3.—Fifty-four-year-old woman with nephrosclerosis. Under the supervision of the clinic for years because of hypertension. Since the end of April, 1929, dyspnea and anginal pain on effort. In May, 1929, an attack of pain lasting fourteen hours, appearing without exciting cause, associated with extreme anxiety and dyspnea. After this, enforced bed rest for eight days. On June 11, 1929, blood pressure 185 mm., specific gravity of urine 1.006 to 1.018, angiospastic neuroretinitis, cardiac

decompensation. Since then constantly under observation in the clinic or as an ambulatory patient because of cardiac insufficiency. She was hypersensitive to strophanthin. Death on August 17, 1930, after several days of anuria from cardiac and renal insufficiency. Autopsy: generalized arteriosclerosis with marked sclerosis of the coronary arteries, particularly the anterior descending ramus, chronic aneurysm the size of a goose egg of the ventricular wall in the region supplied by this vessel; definite fibrous scarring of the heart and adherent pericardium; nephritis with marked shrinking of the glomeruli, and sclerosis of the afferent vessels.

Electrocardiograms. Fig. 3a shows the electrocardiogram four years before the insult, typical left axis deviation. A year later the picture was the same. Extrasystoles, always of the form shown, were observed for years. Fig. 3b shows the picture six weeks after the attack and was the form which persisted until death fifteen months after the attack. The R-wave of Lead I has become widened, splintered and of low voltage, while the Q-wave is even more prominent. A noteworthy change in the form of the ventricular extrasystoles has occurred. In a large collection of material we have seen only one other case—also a case of coronary thrombosis—in which there were such changes in the form of the premature beats.

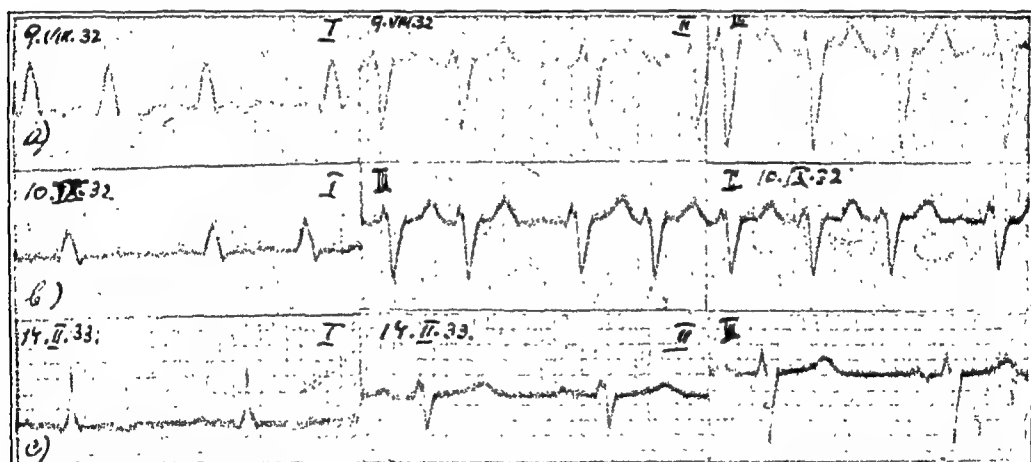


Fig. 4.—Case 4, attack August 4, 1932.

Summary. Clear-cut old myomalacia in the region supplied by the anterior descending ramus in a patient with hypertrophy of the left side of her heart and nephrosclerosis. The characteristic dwarfing of R_1 appeared six weeks after the attack and persisted until death, fifteen months after the attack. Unquestionable changes in the form of the extrasystoles, which presumably arose from the same focus, appeared after the attack.

CASE 4.—Fifty-four-year-old housewife, in good health until August 4, 1932. On the afternoon of this day a sudden attack of vertigo forced the patient to lie down. A few hours later she had an extremely violent attack of pain associated with collapse and followed by dyspnea and fever. Admitted to the clinic August 6. Temperature 38.4°, blood pressure 120/80 mm., right hydrothorax, signs of pulmonary edema, heart somewhat dilated with feeble impulse a fingerbreadth outside midclavicular line, heart sounds feeble, systolic murmur at apex, pulse scarcely palpable, rapid and irregular. Recovery was interrupted by an attack of auricular

fibrillation on August 9 and 10. On August 12 auricular flutter which, because of the rapid ventricular rate (190 with two-to-one block), seemed to threaten life but which was overcome with quinidine, 0.8 gm. Further course uneventful. Blood pressure on August 29 was 95/70 mm. but later rose to 110/75. X-ray examination showed a dilated heart without characteristic form.

Electrocardiograms. Fig. 4a shows auricular fibrillation. In Lead I the form of T is so affected by the fibrillary waves that from it alone one could hardly make a diagnosis of coronary thrombosis. The initial complex shows a left axis deviation with R_1 smaller than S_2 or S_3 . The decrease in size is even more apparent in Fig. 2b, taken six weeks after the insult. Six months after the attack (Fig. 4c) the R-waves had increased in size, and sinus rhythm had been reestablished.

Summary. A case of coronary thrombosis, without question from the clinical course, showed in its acute stages T-wave changes which

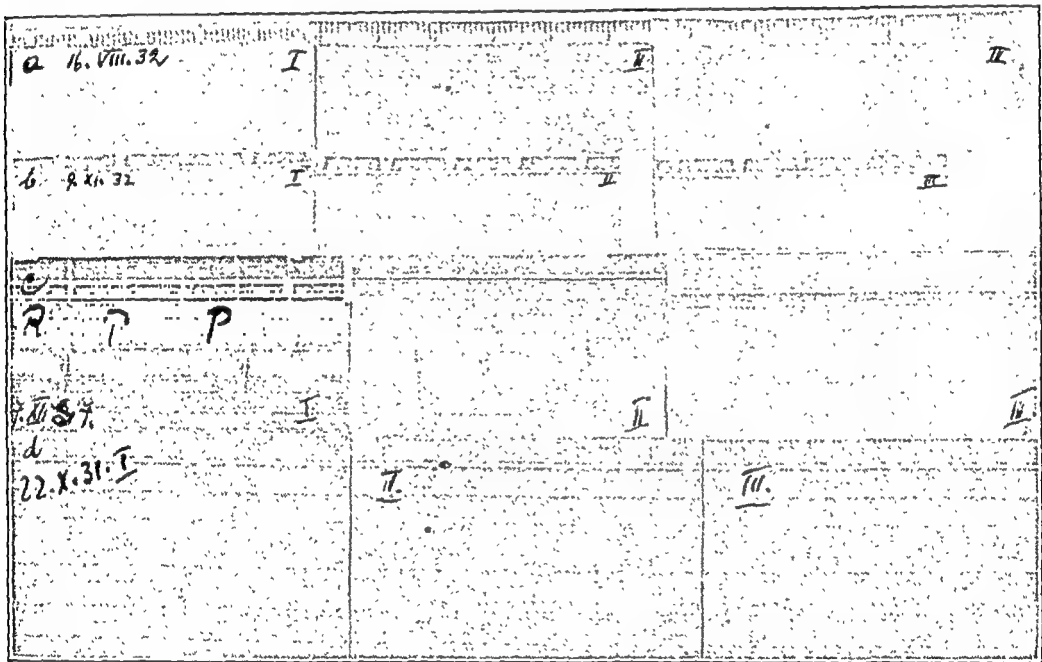


Fig. 5.—(a, b) Case 5, attack November 6, 1932.

(c) Case 8, attack November 13, 1927.

(d) Case 9, attack in May, 1931.

were only suggestive, while the changes in the initial complex, low R_1 together with deep S_2 and S_3 , were definite. Return of normal R_1 six months after the attack.

CASE 5.—Forty-nine-year-old office worker. In January, 1929, began to suffer from nocturnal anginal distress. Symptoms soon appeared on walking but were never paroxysmal in character. In August, 1929, he entered the hospital because of an exacerbation of the symptoms. Except for distant heart sounds there were no abnormal cardiac findings. Blood pressure 130/75 mm. Unexplained elevation of temperature. Good effects from luminal and hormocardiol. After discharge he returned at once to his work (which involved much stair climbing) and almost immediately was attacked by sternocardia and epigastric pain. On the night of November 6, 1932, he was awakened by a terrific attack of pain associated with

angor animi and sense of suffocation. The next day he was moved, in a state of collapse, still with severe pain, and with a temperature of 38.6°. After a short period of improvement the picture was complicated by extrasystolic ventricular tachycardia with a rate of about 150. He died November 17. Autopsy: high grade sclerosis of coronary vessels, almost complete old closure of circumflex branch of left coronary, old malacia of the posterior wall of the left ventricle, closure of anterior descending branch in its upper third with recent necrosis of the anterior wall of the left ventricle from basal portion to the apex, scarring of the septum, eccentric hypertrophy of the right side, chronic passive congestion.

Electrocardiograms. Fig. 5a is one of many electrocardiograms taken between August 22, 1929, and August 16, 1932. All showed a picture, not at all striking, of left axis deviation with relatively low waves, flat T and slight slurring of S in Leads II and III. Fig. 5b, taken three days after the second attack, shows a small Q_1 followed by a reduced R, but only slight decrease in the size of S_2 and S_3 . T₁ shows an upward convexity. In the following days, with the decreasing size of all waves, R₁ disappeared almost completely.

Summary. Two attacks of coronary thrombosis, the first involving the circumflex and leaving no clear-cut electrocardiographic evidence.

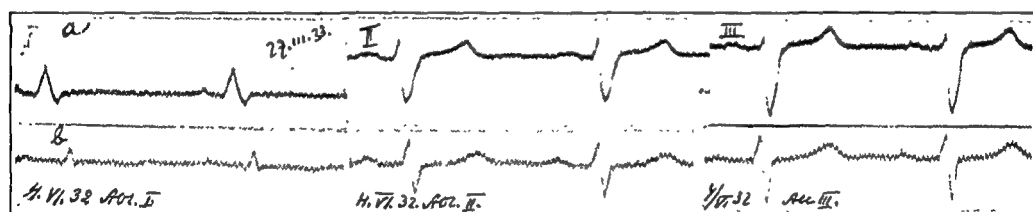


Fig. 6.—(a) Case 6, time in 1/20 sec.
(b) Case 7, four days after the attack.

Three years later occlusion of the anterior descending ramus led to malacia and in the electrocardiogram almost complete disappearance of R_1 while S_2 and S_3 remained relatively well formed.

CASE 6.—There is little information concerning this case, that of a sixty-seven-year-old man who visited the clinic only once as an ambulatory patient. For several months he had suffered from arthritis of the left shoulder and complaints interpreted as anginal. Electrocardiogram was taken because the fluoroscopic picture showed a striking deformity of the left side of the heart interpreted as an aneurysm of the ventricle. Blood pressure 160 mm. Hg.

Electrocardiogram. Fig. 6a shows a record made with Sieman's oscillograph. In all leads QRS is widened to approximately 0.12 sec., but lacks the great size and bizarre form characteristic of complete bundle-branch block. The small R_1 contrasts sharply with the deep S_2 and S_3 .

Summary. Clinical and roentgenological findings to support the diagnosis of aneurysm of the wall of the left ventricle, broad left form of electrocardiogram with striking decrease in R_1 compared with deep S_2 and S_3 .

CASE 7.—Fig. 6b was derived from a seventy-three-year-old patient and was taken outside. According to the report of the attending physician the patient had had a typical attack of coronary thrombosis four days earlier. Blood pressure was normal before the attack.

Electrocardiogram. Another record showing left axis deviation but in this case definite R-waves are present in Leads II and III. Contrast the tiny R_1 with the well-marked S_2 and S_3 . T_1 inverted. P-R interval 0.20-0.21 sec.

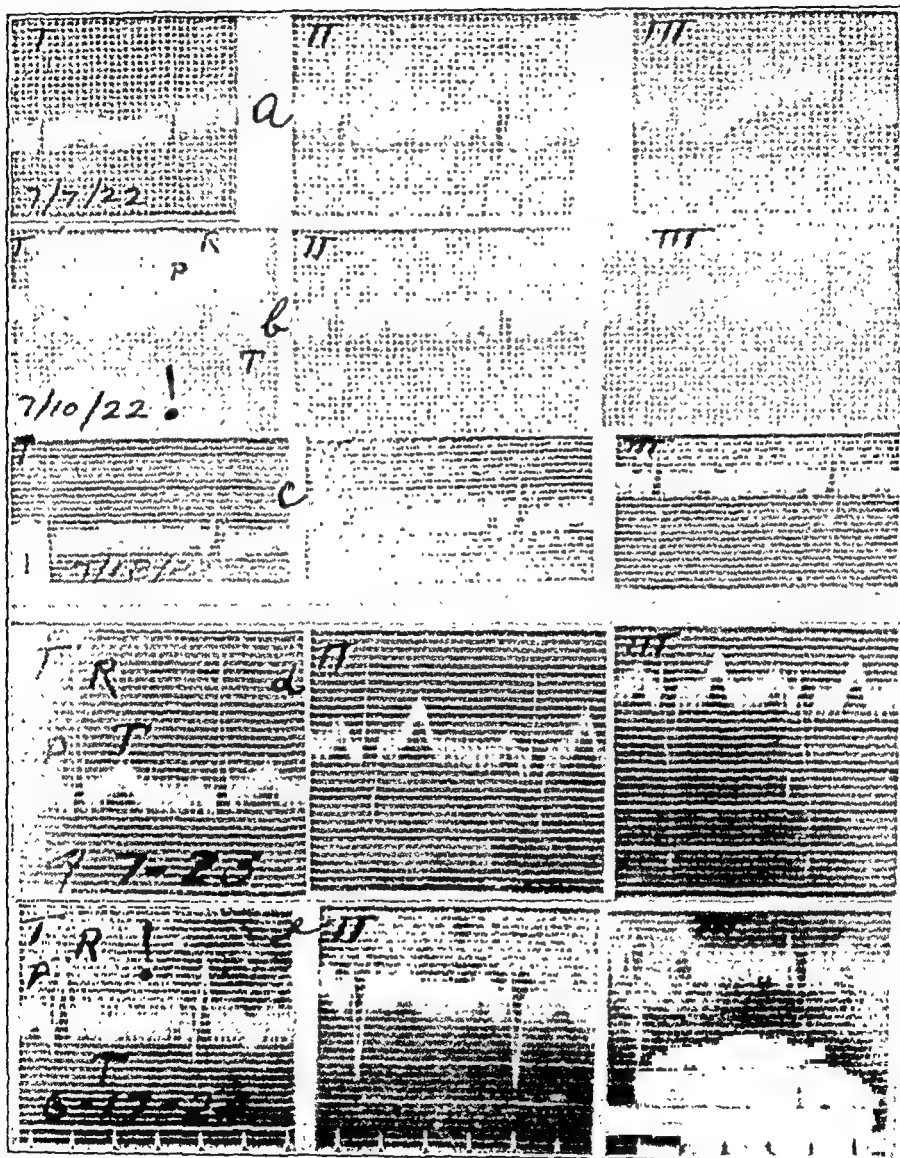


Fig. 7.—Taken from Levine, Figs. 1 and 6.

(a-c) Attack July 6, 1922, good recovery.

(d, e) Attack April 8, 1923, death three years later, no autopsy.

Summary. Four days after acute coronary closure the electrocardiogram suggests myocardial infarct because of the contrast between a diminutive R_1 and a clear-cut S_2 and S_3 .

We shall consider with these cases several definite cases of coronary thrombosis taken from the literature and belonging in the same group.

Levine¹² in his monograph cites 82 incontestable cases of coronary thrombosis in which electrocardiograms were taken, in some cases both before and after the attack. Of these cases 12 belong in our group, those shown in Levine's Figs. 1, 4, 6, 8, 17, 30, 41, 43, 61, 70, 76 and 77. Figs. 7 to 10 are reproductions from Levine's classic material. In three cases one can follow the development of the changes from simple left axis deviation. Five cases were controlled by autopsy

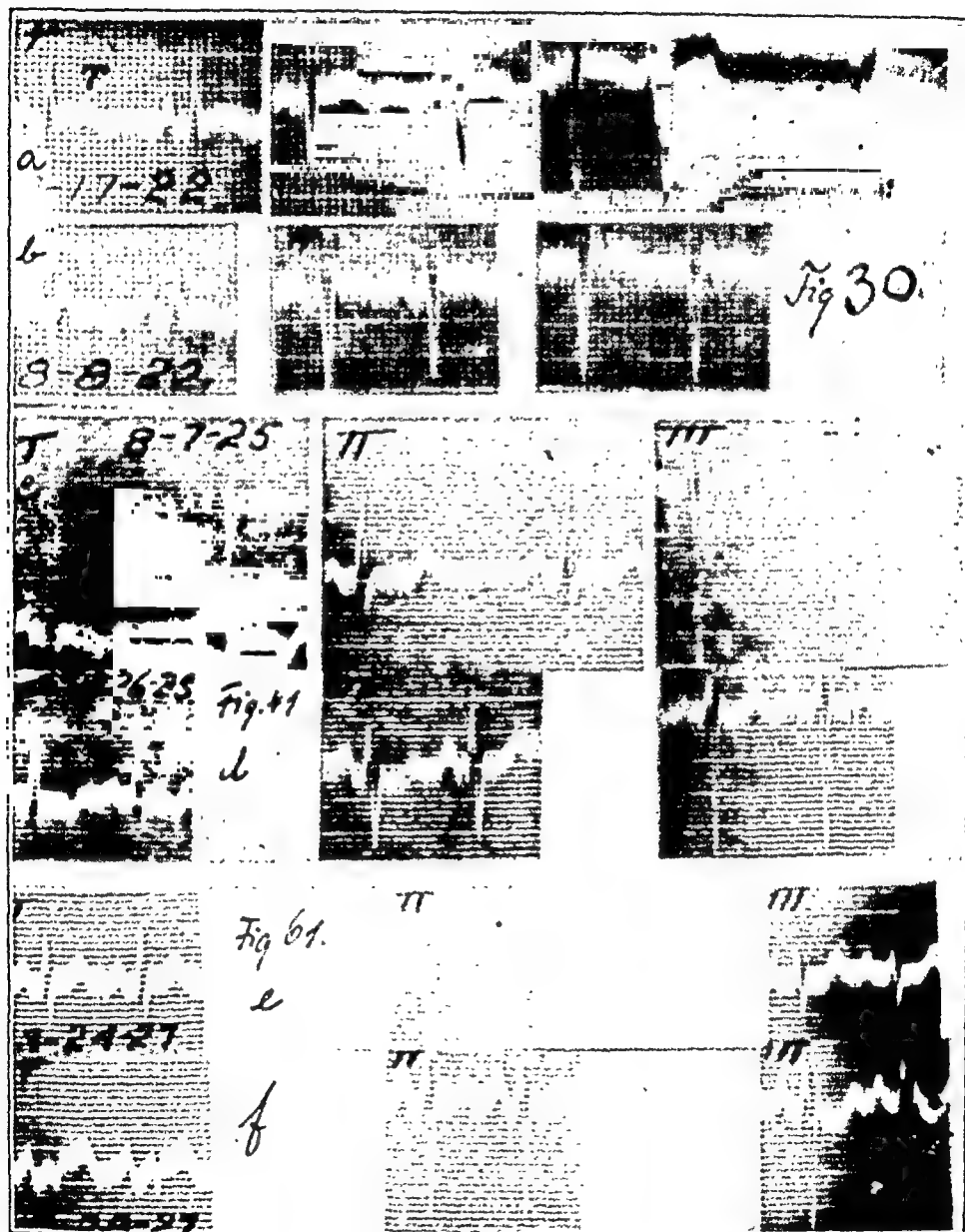


Fig. 8.—From Levine, Figs. 30, 41, 61.

- (a, b) Attack July 4, 1922, death August 8, 1922, infarct of the left ventricle with rupture.
- (c, d) Infarct August 25, 1925; death August 31, 1927. Mesaortitis, stenosis of ostia of coronary vessels, acute infarct of the left ventricle. According to Levine, "Electrocardiogram without definite changes." Note S-T in Lead II!
- (e, f) Attack March 20, 1927, good recovery in spite of paroxysmal ventricular tachycardia.

and infarction of the left ventricle was found in all. In three cases the anterior descending ramus of the left coronary artery was the site of the thrombosis, and in two cases the location of the closure was not mentioned. In two cases there was definite aneurysm of the ventricle in the area supplied by the occluded vessel. Fig. 10c is taken from Dressler's¹³ atlas and shows the same type of case. The author noted that the tracing was from a case of luetic aortic aneurysm and that it resembled the tracings seen in cases of coronary closure. As a matter of fact the appearance of T_1 strongly suggests the presence

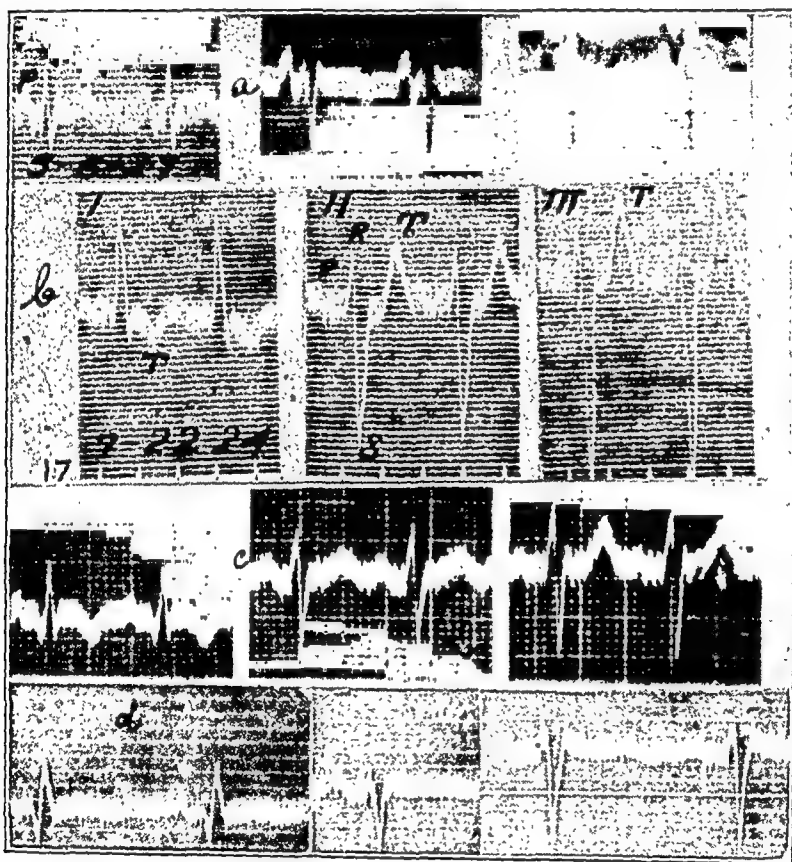


Fig. 9.—(a-c) From Levine, Figs. 4, 17, 43. (a) Attack May 2, 1927. Wassermann reaction +++, good recovery. (b) Attack July 20, 1924: autopsy, thrombosis of anterior descending ramus. (c) Attack November 26, 1926, recovery, later death without autopsy. (d) From Freundlich, Fig. 11. Three months after attack.

of luetic coronary occlusion with resulting myomalacia. In Fig. 73 of his book Mahaim⁸ shows the tracing of a case which was confirmed by autopsy and which is here reproduced in Fig. 10d. Autopsy showed embolic (?) closure of the anterior descending ramus with typical localized infarct and aneurysm of the heart wall. We shall return to the histological picture later. Fig. 10e, taken from Condorelli's book,¹⁴ is derived from a case of coronary thrombosis which showed at autopsy closure of the left coronary with infarct in its area of distribution. In one of Smith's¹⁵ cases (his Fig. 3) the record taken a

few days after the attack shows a picture similar to that which we have illustrated in Figs. 1 to 5. Autopsy showed closure of the anterior descending ramus and of two smaller branches of the circumflex ramus with definite myomalacia at the apex of the left ventricle. In Oettinger's¹⁶ work we find that the case illustrated in Figs. 3 to 6 belongs

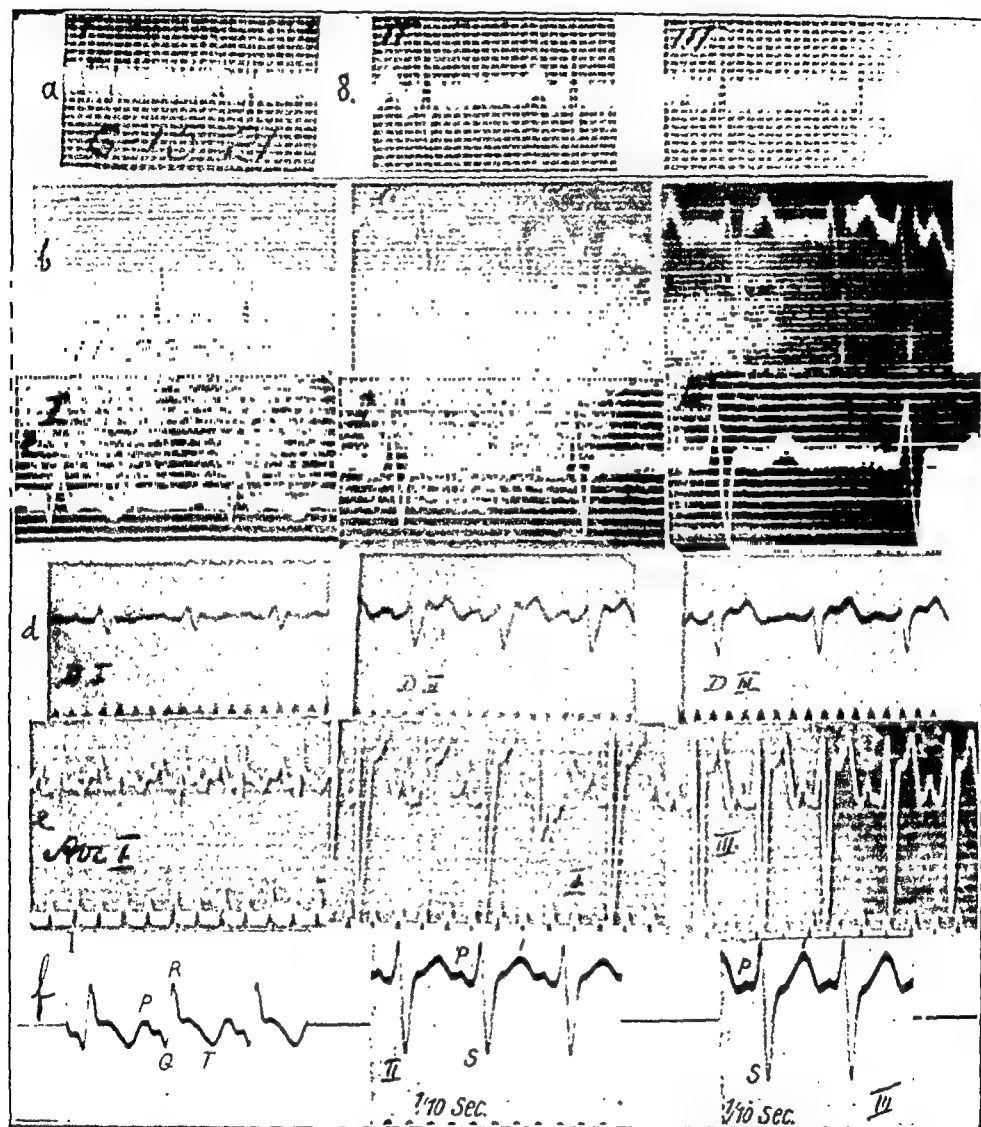


Fig. 10.—(a) Levine, Fig. 8. Attack June 10, 1921; death June 22; blood pressure had been 200.
 (b) Levine, Fig. 77. Attack October 18, 1923, death December 3, 1923, almost complete closure of anterior descending ramus.
 (c) From Dressler, Fig. 22 (see text).
 (d) From Mahaim, Fig. 72 (see text).
 (e) From Condorelli, Fig. 67. Seven months after the attack, seven days before death, thrombosis of the left coronary artery, large infarct of the apex and anterior wall of the left ventricle.
 (f) Oettinger, Fig. 6. Thrombosis of the anterior descending ramus.

in our group (see Fig. 10f). This also showed occlusion of the anterior descending ramus post mortem. Also in the recent work of Freundlich¹¹ we can recognize in Figs. 11 and 12 (see Fig. 9d) similar changes

in the QRS group. This tracing came from a case of severe angina pectoris three months after coronary closure. We are convinced that further examination of the literature would reveal still more cases of this sort.

The second group, to which we shall now pass, is closely related to the first. The first two cases mark a direct transition.

CASE 8.—A forty-three-year-old official arrived on November 13, 1927, after a tiring motor trip to visit his wife in a sanatorium. On the way he had had a violent attack of stenocardia which had forced him to interrupt his trip and to rest for several hours in a hotel room. The physician who was called stated that the temperature was 36.5°, pulse 120 and small, cardiac dullness normal. The pain disappeared after medication. On November 15 x-ray examination showed the heart at the anterior axillary line, temperature 38.6°. Patient was admitted to the clinic on November 28. His father had died of a heart attack and one brother of heart disease. He smoked 20 cigarettes a day, used alcohol to excess, denied syphilis. Wassermann reaction was negative in the blood and spinal fluid. Heart dullness normal, scratchy systolic murmur at Erb's point. On x-ray examination the shape of the heart was not characteristic, greatest transverse diameter 13.5 cm. Blood pressure 105 mm. No pain.

Electrocardiogram. Fig. 5c shows in Lead I a deep Q-wave followed by an R of the same height; T-wave shows bowing above the isoelectric line and is inverted. Leads II and III show small R- but deep S-waves; T₂ and T₃ not striking. QRS is of normal duration.

Summary. Clinically this was certainly a case of coronary thrombosis. Four weeks after the attack the electrocardiogram showed suspicious changes in the final complex in Lead I, and an initial complex with the main deflection downward in all leads.

CASE 9.—A fifty-four-year-old mason was taken sick in May, 1931, with anginal distress. The individual attacks were of short duration, not very violent, repeated more than ten times in one day. After several days' rest in bed he returned to work but experienced anginal pain on effort. On August 22, 1931, he noted edema for the first time. In September he had cardiac asthma that did not recur after digitalis. From then on he had permanent decompensation and attacks of angina. Blood circulation time (decholin method) 38 sec. (normal up to 16 sec.). X-ray examination showed the heart to be dilated to both sides but without characteristic form. Faint heart sounds. Blood pressure 85 mm. Under constant observation, last seen in January, 1933.

Electrocardiogram. Fig. 5d. The picture is very similar to that of the preceding case. Again there is a deep Q in Lead I and the chief deflection is downward in Leads II and III. The R-T segment is so uncharacteristic that from it alone the diagnosis of coronary thrombosis could not be made. Three months later, about eight months after the onset, the electrocardiogram was practically unchanged.

Summary. Gradual development of myomalacia of the left ventricle. Following the attack and eight months later the initial complex of the electrocardiogram was directed downward in all leads. The final complex hardly suggested infarction.

CASE 10.—Fifty-four-year-old working woman. Brief attacks of pain in the region of the heart commenced in February, 1932, became more frequent; and on March 30 there was a very severe attack of pain and oppression. On April 10 a most intense attack associated with vomiting, fear of death, and cold sweat. Findings on April 13, patient in grave state of collapse without edema; left arm and side of chest felt warmer than the right, tenderness over areas supplied by the left trigeminal nerve and brachial plexus. Severe precordial pain which decreased after camphor given intravenously. On April 20 the patient, who had been progressing well, had an attack of auricular fibrillation which stopped spontaneously. After this, hemiplegia. Death on May 1. Autopsy: marked general arteriosclerosis, particularly of the cerebral, sacral and mesenteric vessels, thrombosis of the anterior descending ramus with resulting area of infarction measuring 8×5 cm., involving the septum and anterior wall of the left ventricle, mural thrombus attached to the ventricular aneurysm, localized adherent pericardium, embolism of right middle cerebral and renal arteries, infarct of spleen.

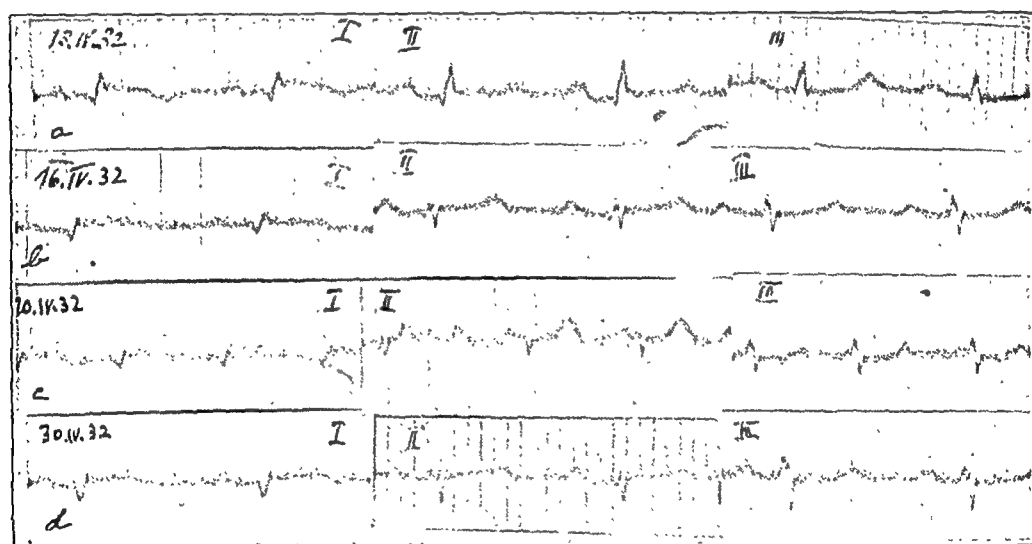


Fig. 11.—Case 10.

Electrocardiograms. In Fig. 11a narrow excursion of all waves, small Q in Leads I and II. T_1 shows high take-off, is prolonged and convex in form. In Fig. 11b waves still smaller, small S in Leads II and III. In Fig. 11c auricular fibrillation with coarse fibrillary waves. In Fig. 11d sinus rhythm restored; R_1 and R_2 absent; initial complex downward in all leads. T-wave permits recognition of the insult only on closest inspection.

Summary. Thrombosis of the anterior descending ramus with the formation of a large aneurysm of the ventricle. The initial complex, at first not characteristic, assumed a characteristic form after seventeen days so that finally it was directed downward in all leads.

CASE 11.—A sixty-year-old business man. Dyspnea on effort since 1923, in 1929 diabetes mellitus established; since the end of 1929 edema at the end of the day. In winter of 1930 massive edema; confined to bed since then. Admitted to the clinic March 30, 1932, with extreme decompensation, pulsus alternans, edema, con-

gestive effusions. On examination feeble impulse in anterior axillary line, heart sounds almost inaudible, blood pressure 150/115 mm. *Cor bovinum* on x-ray examination. A fair diuresis with novurit and ammonium chloride. Allowed to go home and died soon thereafter.

Electrocardiogram. Fig. 12a. The initial complex shows slight notching in the first two leads, no R in Leads II and III, S relatively well defined in all leads. T-waves are almost isoelectric, suggesting poor compensation. Duration of QRS is 0.09 sec. P-R interval is 0.1 to 0.12, and there is no isoelectric line between P and R.

Summary. A badly damaged heart, apparently as the result of hypertension. The electrocardiogram failed to show the expected left axis deviation, and the initial complex was directed downward in all leads.

CASE 12.—A seventy-four-year-old guide on March 19, 1932, while walking was seized with an attack of severe breathlessness and cough which disappeared after he

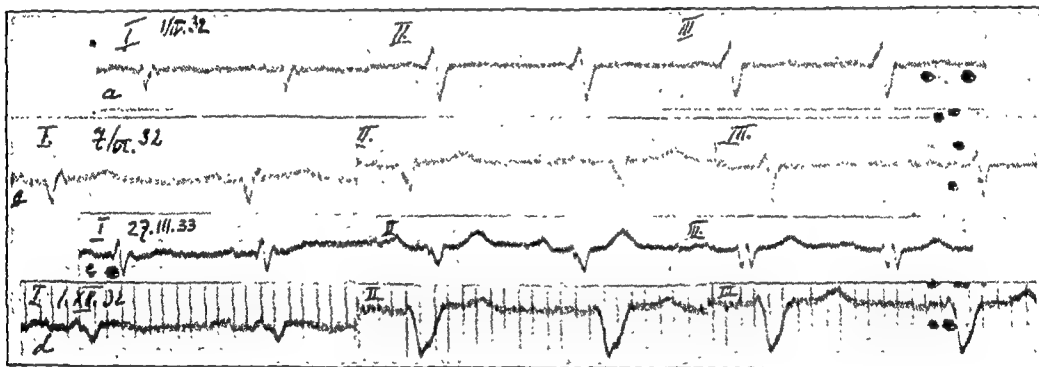


Fig. 12.—(a) Case 11.

(b) Case 12. Attack March 19, 1932; death January 10, 1933; large aneurysm of the anterior wall of the left ventricle.

(c) Case 13. Attack October 19, 1932.

(d) Case 14. Attack October 13, 1932.

had stood still for a few minutes. That night he had a severe attack of dyspnea with violent anginal pain "as if his heart was being crushed with red hot pliers." The attack lasted three hours. After this he had orthopnea at night and in the middle of May edema. On June 6, 1932, he was admitted to the clinic in a state of severe decompensation. He was found to have a heart dilated to left and to right, without characteristic form, distant dull sounds without accentuation, blood pressure of 180/105 mm. emphysema, Wassermann reaction negative. Death occurred on January 10, 1933, apparently from cardiac insufficiency. Autopsy: high grade coronary sclerosis with marked stenosis of the anterior descending and circumflex branches of the left coronary artery, old aneurysm measuring 10×5 cm. involving the septum and apex of the left ventricle, marked sclerosis of the aorta, chronic passive congestion.

Electrocardiogram. Fig. 12b shows one of several electrocardiograms taken at various times. R-wave completely absent in Leads I and II, rudimentary in Lead III. S-wave present in all leads, notched in the second. In Lead I, S is followed by a small positive deflection that might be called R, in which case S might be described

as a deep Q. In any case the principal deflection is downward in all leads. T_1 and T_2 are upright. T_3 is shallow and inverted but not characteristic. QRS is of normal duration.

Summary. Badly decompensated heart with area of myomalacia three to eight months after acute coronary closure, narrowing of anterior descending and circumflex branches with aneurysm. The initial complex of the electrocardiogram directed downward in all leads, but apart from this no electrocardiographic evidence pointing to infarction.

CASE 13.—Forty-eight-year-old factory manager, formerly well, heavy cigarette smoker. On the evening of October 19, 1932, after straining at stool, had terrific attack of precordial pain which lasted one hour and was associated with sweating and fear of death. One week later nocturnal return of pain leaving him very weak for two or three days. Since then angina on effort and exhaustion on the least exertion, but comfort when at complete rest. On March 27, 1933, no abnormal findings on physical examination, blood pressure 125/70 mm.

Electrocardiogram. Fig. 12c. At this time the patient was taking small doses of digitalis. The R-wave is apparent only as a small notched elevation in Lead I, absent in the other leads. S is low but definite in all leads, moderately splintered in Lead II, and grossly splintered in Lead III to form a W. QRS is of normal duration. The slight depression of S-T and T in Lead I is not remarkable and may be the result of digitalis.

Summary. From the clinical course a coronary thrombosis with secondary myomalacia is most probable. Electrocardiograms five months after the attack and later showed no characteristic changes in the final complexes. The initial complex shows, together with low voltage and notching without widening, a definite preponderance of the negative as compared with the positive waves.

CASE 14.—Sixty-three-year-old pensioner. For four years angina on effort and dyspnea while working. On the evening of October 13, 1932, after leaving the inn where he had consumed two liters of beer, he had violent cramplike pain in the epigastrium extending upward under the manubrium and lasting twelve hours. The next day he walked to the office of his physician, who found that the blood pressure which formerly measured 160 mm. had dropped to 95 mm. On the way home another attack of pain prevented him from continuing on foot. He got up after a week in bed, but felt very weak and was short of breath on slight exertion. On December 1, while returning from a visit to his physician, he had a severe attack of cardiac asthma in which he was brought to the clinic. Family history not remarkable. He did not smoke more than 12 cigarettes, denied syphilis. Examination showed a heart enlarged to the left, feeble sounds and definite gallop at the apex, blood pressure 115 mm., temperature normal, leucocytes 14,000, aortic configuration of heart on x-ray examination and on the left border a bulging which showed slight pulsation (aneurysm).

Electrocardiograms of November 17, December 1, 2, and 4, were practically identical and showed (Fig. 12d) sinus rhythm, normal P and P-Q, QRS duration of 0.13 sec. The principal deflection is downward in all leads, initial complex very

low and somewhat notched in Lead I; in Leads II and III a moderately deep S-wave with definite notching of the up-stroke. The S-T segment is somewhat above the isoelectric level in Leads I and II, but this is significant only in Lead I, since T is inverted in this lead. In Lead III there is some change in the S-T segment as S fails to reach the isoelectric line, a change often associated with bundle-branch block.

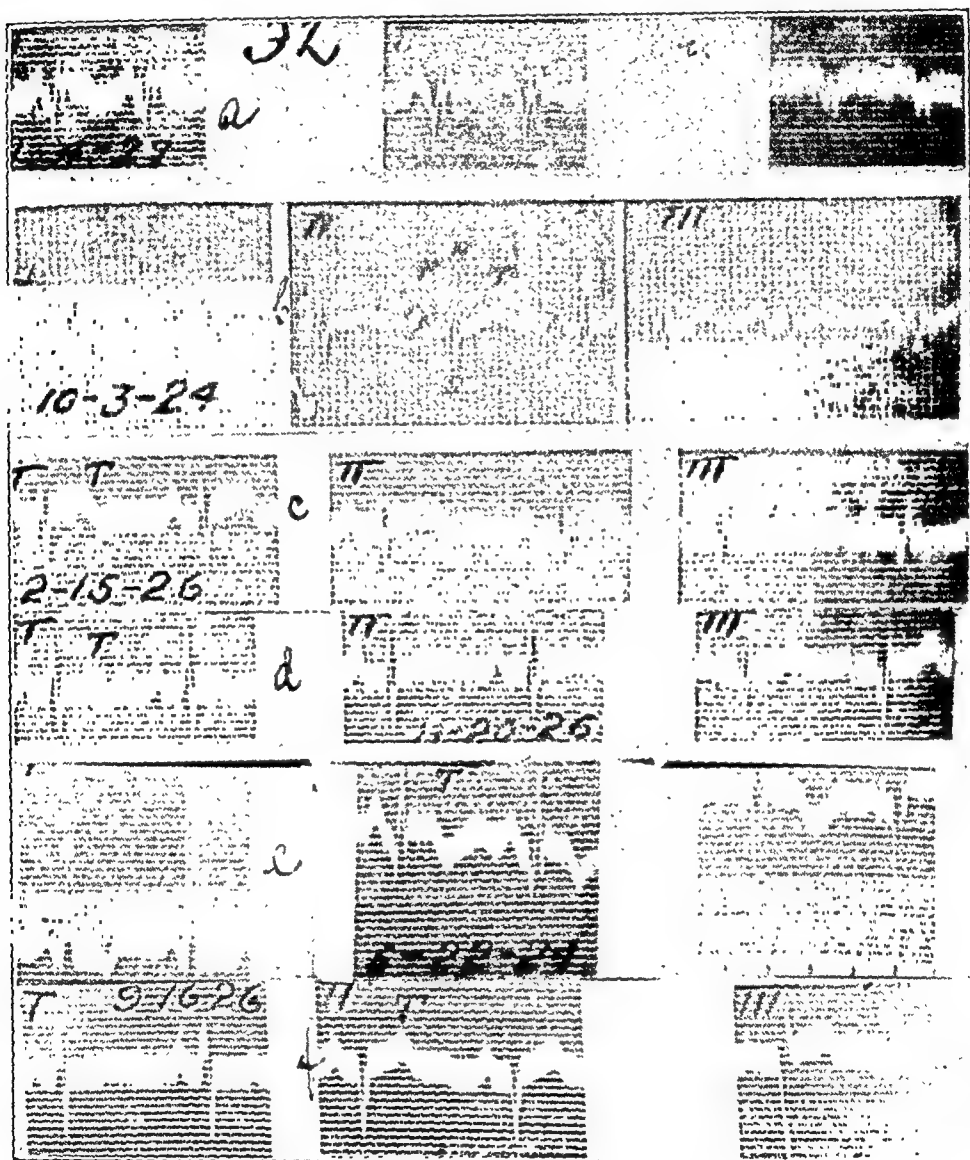


Fig. 13.—From Levine, Figs. 32, 36, 44b, 44e, 40a, 40h.

(a) Attack December, 1927; autopsy, thrombosis of anterior descending ramus. (b) Attack June 21, 1924, recovery. (c) (d) Attack February 4, 1926, recovery, persistence of Type b-rs for a long time. (e) (f) Attack June 17, 1924; autopsy, thrombosis of anterior descending ramus, aneurysm of heart wall. Gradual appearance of Type b-rs.

Summary. Clinically and roentgenologically there is little doubt that this was a case of coronary thrombosis with a large aneurysm of the left ventricle. Electrocardiograms, five to seven weeks after the attack, showed a severe disturbance of intraventricular conduction

and a preponderance of all the negative waves of the QRS group, but in the final complex only a suggestion of the changes associated with coronary thrombosis.

We can also add to this group several examples from the literature. Fig. 13 is a reproduction from Levine's monograph. In all four cases there was unquestionable coronary thrombosis which in the cases represented by Fig. 13 *a* and *c* was found at autopsy to involve the anterior descending ramus. Of particular interest is Case 13 *c, d* which, eleven days after the insult (*c*) still showed typical left axis deviation, while the characteristic changes did not appear until one month after the insult nor did they show complete development for two months more.

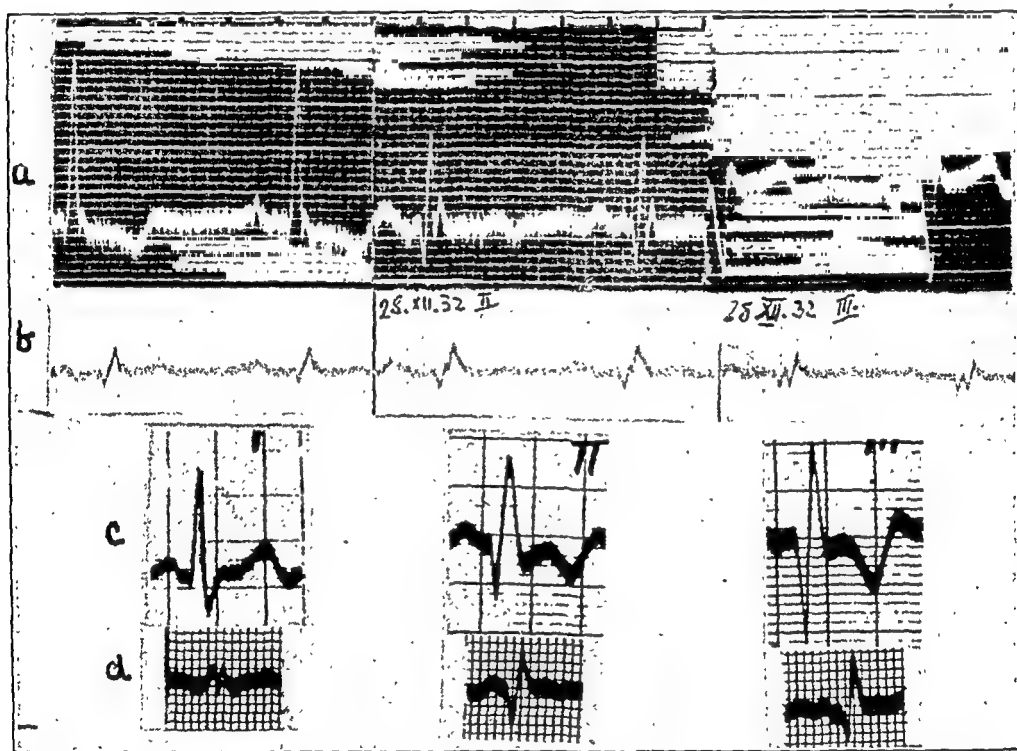


Fig. 14.—(*a, b*) Case 14. Before and after the second attack on December 24. (*a*) With Boullitte's string galvanometer, (*b*) with the Sieman's oscillographic machine. (*c, d*) From Cooksey and Freund, Fig. 4*a* and *f*. Three weeks after the first attack and forty-eight hours after the second (see text).

Smith¹⁵ in his paper shows a striking case in which one month after coronary closure the initial complex was directed downward in all three leads. (See Fig. 4*b* of Smith's article.)

In its final picture the last group is less sharply defined than either of the foregoing. It is noteworthy, however, for the fact that changes in the preexisting electrocardiogram appear suddenly, almost without transitional steps, following the coronary closure.

CASE 15.—A sixty-five-year-old retired official who had suffered from steno-cardial oppression for a long time was admitted to the clinic on December 25, 1932,

in a state of collapse with severe dyspnea. For a time he complained of painful sense of pressure in his chest which interfered with breathing. He had no edema, some cyanosis, respirations thirty with a suggestion of periodic character. Other physical findings negative except for faint heart sounds, blood pressure 125/80 mm. Wassermann reaction negative. After strophanthin and hexeton intravenously he had relief from pain and dyspnea. Still his condition remained grave, and on December 31, twenty minutes after the injection of strophanthin, 50 mg., he became intensely cyanotic, stopped breathing and died. Autopsy: marked sclerosis of the arteries at the base of the brain and of the coronary and abdominal vessels; thrombosis in its middle third of the circumflex branch of the left coronary; almost complete closure in the upper and complete closure in the middle third of the anterior descending branch; scar, measuring 4x5 cm., on the posterior wall of the left ventricle and recent softening of the lower third of the anterior wall, the apex, and the lower part of the septum extending to the lower part of the right ventricle; mural thrombus attached to the infarcted area; thrombi in the periprostatic plexus, thrombosis of the spleen, recent portal thrombosis; embolism to pulmonary artery supplying right upper lobe; chronic passive congestion; hypertrophy of right ventricle.

Electrocardiograms. Fig. 14a is a record taken two months before death, apparently after the first attack involving the circumflex ramus and before the second attack involving the anterior descending ramus. These records were taken with Boulitte's string galvanometer, and we are indebted to Dr. E. Weitels for his courtesy in allowing us to reproduce them. The tracing shows typical left axis deviation with large excursions. In Lead I there is a suggestion of a Q-wave, while Q is definite in Lead II. Since S_2 is preceded by no R, it would be interpreted as a deep Q-wave according to Pardee. The terminal portion of R_1 and R_2 shows splintering. QRS width is normal. R-T interval is below isoelectric level in Lead I, above it in Lead III. Still from our own experience we would prefer not to consider this record indicative of recent coronary thrombosis but to compare it with Fig. 1 as an expression of left axis deviation. Rather it seems to us that the appearance of Q_2 indicates old infarction on the posterior wall of the heart. Fig. 14b is a record taken with the oscillogram three days before death. It shows fundamental changes in all leads. The high waves have been replaced by deflections of very low voltage. Q_1 and Q_2 persist. The rudimentary R_1 still shows the terminal splintering; R_2 has likewise almost disappeared, but its terminal part retains the same form. In Lead III the deep S or Q is replaced by a little W. R-T in Lead I now shows definite elevation above the isoelectric level, while S-T is depressed in the third lead.

Summary. Old thrombosis of the circumflex and recent thrombosis of the anterior descending ramus with localized areas of malacia. While the electrocardiogram before the second attack showed left axis deviation with high voltage, after the closure of the anterior descending ramus a marked reduction of all waves gave the picture of low voltage. Certain portions of the curve remained unaltered.

We find a similar case in Levine's paper. In Fig. 29, taken three days after closure, there is marked left axis deviation. From the fourth to the eighth day this yields to low voltage through a lowering of R_1 , R_2 ; and S_3 . The form of the waves is retained. On the tenth day the original form reappears. This differs from our case in that

there is certainly a disturbance of intraventricular conduction (according to Levine in the right branch?). Then on the seventh day the small and normal complexes alternated, according to either a lengthening of the recovery time (normal waves) or a shortening of conduction (small waves). In the same group belongs a case described by Cooksey and Freund¹⁷ which at autopsy showed an old, partially canalized thrombus of the right coronary artery and a recent closure of the anterior descending ramus with a large infarct of the anterior wall of the left ventricle (Fig. 14 *c* and *d*).

COMMENT

If we assemble the essential facts of the three groups, we find the following results. In the first group are reported 7 of our own cases and 19 cases from the literature. In all which came to autopsy the diagnosis of coronary closure was verified, invariably affecting the left ventricle and, where noted, the anterior descending ramus. The diagnosis in those cases which did not come to autopsy was established on clinical and electrocardiographic evidence. The characteristic common to all is the change in the initial complex of the electrocardiogram. In Lead I there is a small R-wave, while S is absent or rudimentary, and Q may be present or absent. Leads II and III are dominated by a deep S-wave which is greater than any of the other waves of any lead. The preexisting electrocardiogram usually showed left axis deviation. The changes may appear immediately or some time after the attack, may persist or disappear, usually last longer than do the changes of the final complex. We shall indicate the changes of this group by the abbreviation "*aBB*," by which we mean that *a* is an upward and *B* a downward deflection of the initial complex and that *a* is a small and *A*, a large deflection.

The second group, which for convenience we shall indicate as *b*₁₋₃, includes seven of our own and five cases from the literature. Two of the former and four of the latter cases were verified post mortem, and in the others severe myomalacia was recognized clinically. In the autopsied cases the anterior descending ramus and the region supplied by it were invariably affected. In this group the electrocardiogram is characterized by the negativity of the principal deflections in all leads. Usually, too, the waves are smaller than normal. The main deflection may be a Q or an S. In the observed cases the electrocardiographic changes appeared only after an interval and persisted. In Levine's Case 44 the R₁ became greater than S₁ nine months after the attack.

The third group is made up of one case which we verified at autopsy and two cases from the literature. The two cases which were examined post mortem showed old thrombosis,—once of the right, once

of the circumflex branch of the left coronary artery—and a recent closure of the anterior descending ramus with resulting infarction. The electrocardiographic changes first appeared after the second closure. Before this attack the electrocardiogram showed left axis deviation with high waves; immediately after this attack there was a prompt decrease in the size of the principal waves in all leads, while smaller deflections retained their characteristic form. The result of these changes is an electrocardiogram with low, slurred and notched waves similar to that described by Oppenheimer and Rothschild⁷ as indicating arborization block. A real widening of the QRS group was found only in Levine's case (see Fig. 29 of his monograph) where there was evidence of definite interference with intraventricular conduction. In this case the electrocardiographic changes persisted for a few days only; in the other cases they lasted to death, which occurred rather promptly. The characteristic of this group is not so much the electrocardiographic picture after the insult as the promptness with which successive changes appear. These cases will escape observation if they are not followed closely as the changes develop.

DISCUSSION

Practically the most important question is whether the changes are pathognomonic so that on their appearance alone one is warranted in making a diagnosis of coronary closure and infarction of the heart. The close association between the changes in the ventricular complexes, the time of infarction and the autopsy findings makes it appear certain that the changes in the initial complex are the result of, and not merely coincidental with, the myocardial changes. Still it is not certain that similar electrocardiographic changes might not occur in other conditions. This possibility cannot be excluded for the end-picture of the third group, for this picture is not sufficiently clear cut. For the pictures of groups one and two we can say, on the basis of clinical experience which is founded on the examination of over 10,000 electrocardiograms at the First Medical German Clinic, that they are certainly uncommon; indeed those of group two (b_{1-3}) are distinctly rare. Particularly in oscillograph electrocardiograms, the appearance of pronounced S-waves is definitely abnormal. In cases of ordinary left or right axis deviation the appearance of S-waves in all leads does not occur. To secure objective evidence on this matter we looked through 1,460 electrocardiograms from different individuals chosen at random from our files and for the most part derived from patients with abnormal hearts. We examined these tracings to select those which showed the following features: (1) electrocardiograms in which S_2 and S_3 were greater than the R-wave of any lead in which R_1 was greater than S_1 , and (2) electrocardiograms in which the principal

deflection was downward in all leads, regardless of whether this deflection was an S or a Q. Of the first group we found 19 cases (1.3 per cent) of which four are included in this report; five others probably had myocardial infarct; two lacked clinical data; and seven gave no evidence for a diagnosis of infarction of the heart. Yet it must be noted that of the seven apparently contradictory cases six differed from our Type aBB in that they showed very low voltage, with S_2 and S_3 smaller than 6 mm. Of the second group we collected eight cases (0.55 per cent) of which four are considered in this study, and two others are suggestive of myocardial infarct; one case lacks clinical data and only one case (congenital anomaly) seems contradictory. Cases of third degree automatism were not included. From these results we conclude that the appearance of an electrocardiogram of Type aBB or of Type b_{1-3} is strongly suggestive, if not absolutely pathognomonic, of myocardial infarct. The same indeed may be said for the "coronary T-wave"; the sharply inverted T and the plateau T may be found in other conditions. Increase in the size of Q_3 can be interpreted only with reservations. While, according to Freundlich,¹¹ the "coronary Q-wave" is always associated with changes in the final complex, the changes in the initial complex which we have described are independent of other electrocardiographic findings, a fact which enhances their clinical value. Levine noted that the cases reproduced in our Fig. 8 c and d showed nothing unusual. Also we find the initial complex to be the only evidence pointing to infarction in Figs. 6a and 12a. It seems probable that *more attention directed to the initial complex will reduce the number of cases hitherto classed as silent coronary thrombosis*. The changes which we have described resemble the other recognized electrocardiographic criteria for the diagnosis of coronary thrombosis in significance but not in frequency.

It is not clear why only a fraction of the cases of true coronary thrombosis shows the changes described in the QRS complex. Two possibilities must be considered. In the first place it is only natural that the form of the electrocardiogram before the insult should influence its further development. In most of the cases cited the pre-existing electrocardiogram showed left axis deviation with fairly high waves as nearly as can be determined. How the QRS changes would manifest themselves if, before the insult, there was right axis deviation or some other type of record, must be determined by further studies. Exceptionally, however, changes of Type aBB or b_{1-3} may appear without earlier left preponderance, as Fig. 11 shows.

The second factor which influences the appearance or absence of changes in the initial complex is the localization and extent of the infarct. It cannot be an accident that all the autopsy protocols showed evidence of infarction of the left ventricle, usually with extensive

myomalacia in the area supplied by the anterior descending ramus. One might object that this localization is the most common one, not only in the cases cited here, but generally. However, if one accepts the statement of Levine, who has most data on this point, that 85 per cent of the cases of coronary thrombosis involve the anterior descending ramus, one would expect from the number of our cases that now and again the thrombosis would have a different site. This is not the case in either group one or group two, whereas in both the autopsied cases of group three there was double thrombosis. On other grounds it appears to us not improbable that different anatomical processes underlie the first two and the third groups. But this argument is not sufficient to explain the absence of the changes in the initial complex in a series of cases. Fig. 7 of Levine's monograph shows clear left axis deviation which remained until death in spite of the fact that autopsy showed an extensive infarct of the anterior wall of the left ventricle.

In an attempt to explain the mechanism underlying the formation of changes in the initial complex after cardiac infarction, we are aware that we enter upon the uncertain territory of theory. We can with certainty exclude the possibility that extracardiac factors, such as change in the position of the heart or altered peripheral resistance, have anything to do with the process. There remain therefore only two other possibilities. Either the changes are the expression of a definite disturbance of intraventricular conduction, or they are the reflection of a change in the dynamic balance of the two halves of the heart.

1. *Theory of disturbance of conduction.* Certainly neither the electrocardiogram of Type aBB nor that of Type b_{1-3} corresponds with the familiar picture of arborization or bundle-branch block. At first glance it might seem that Type aBB could be considered as a modification of the usual form of bundle-branch block (so-called right bundle-branch block). The assumption of a block situated so high is incompatible with the anatomical localization; since usually it is only the lowest part of the intraventricular septum which is involved in the necrosis. For the acceptance of intraventricular or bundle-branch block one requires a delay in intraventricular conduction time, and for a disturbance of both branches one must have a prolongation of the P-R interval. Such a condition was present only once in all our material. As to the increased duration of QRS as the expression of a delay in the spread of the excitatory process through the ventricles, the following table shows the results found in our cases. In Table I is shown the greatest duration of the initial complex in any one of the three usual leads.

TABLE I
THE GREATEST WIDTH OF THE INITIAL COMPLEX IN ANY LEAD OF THE
ELECTROCARDIOGRAM

CASE	BEFORE ONSET OF QRS CHANGES	DURING PERIOD OF CHANGES	AFTER RECOVERY
Type aBB			
Case 1	—	0.105	0.12
2	—	0.10	—
3	0.12	0.115	—
4	—	0.09	0.08
5	0.095	0.095	—
6	—	0.12	—
7	—	0.08	—
Levine, 1	—	0.10	—
8	0.06	0.08	—
17	—	0.10	—
30	—	0.095	—
43	—	0.095	—
76	—	0.10	—
77	—	0.115	—
Dressler	—	0.10	—
Freundlich, 11	—	0.09	—
12	—	0.095	—
Mahaim	—	0.10	—
Condorelli	—	0.10	—
Oettinger	0.08	0.10	—
Type b ₁₋₃			
Case 8	—	0.08	—
9	—	0.09	—
10	0.07	0.07	—
11	—	0.09	—
12	—	0.09	—
13	—	0.08	—
14	—	0.113	—
Levine, 36	—	0.075	—
44	—	0.085	—
Type c ₁₋₃			
Case 15	0.12	0.10	—
Levine, 29	0.10	0.12	0.10
Cooksey	0.11	0.08	—

Two things must be considered in interpreting these figures. It is possible that the widening of the initial complex is dependent on a preexisting and unrelated bundle-branch disturbance, as in Cases 3 and 15 in which before the onset of the coronary thrombosis the initial complex was widened to a duration of 0.12 sec. On the other hand, the degree of widening of the QRS complexes which is found in Table I is not definite proof of interruption of the path of conduction through a bundle branch, for we may find such slight change in cases of marked hypertrophy.¹⁸ If, in our series of 31 cases, we find the duration of QRS to be less than 0.1 sec. in sixteen cases, just 0.1 sec. in nine, and more than 0.1 in seven, we are certainly not justified in drawing any conclusions as to the importance of widening of QRS as one of the criteria of the changes in the initial complex or as to the existence of a disturbance of conduction in all these cases.

Histological studies of the conducting fibers of appropriate cases would be of help in solving the problem. Unfortunately we did not make serial sections of our cases, nor does Levine's material have this information. Only in Mahaim's⁸ case were there satisfactory histological studies. As a matter of fact examination of his case (see our Fig. 10d) showed complete interruption of the right branch and partial destruction of the left. He attributed the electrocardiographic changes to this lesion of the conducting system. We do not feel that we can draw final conclusions from this isolated case, especially as the P-R interval was normal as opposed to the histological picture.

Regarding the great difficulty in making, and the caution required in interpreting, histological studies of the heart, we refer to the judgment of such experienced investigators as Lewis.¹⁹ Even regarding the laborious and precise studies of Mahaim some doubt arises. In the case in question the cause of the infarct is given as a septic embolism occurring in the presence of open foramen ovale, which seems incompatible with the history of increasing decompensation for one year as well as with the macroscopic picture of the usual ventricular aneurysm with adherent pericardium but no evidence of infection. Elsewhere in Mahaim's work doubt arises over the agreement of histological findings with incorrect electrocardiographic diagnoses. Thus on page 169 in a case of ventricular rhythm in complete block he interprets the form of the beats arising in the ventricle to a coexisting bundle-branch block which seems quite unlikely. Moreover, the histological picture is opposed to the diagnosis of bundle-branch block. In Fig. 30 (p. 120) he shows an illustration of complete block in which the auricular rate is somewhat less than twice the ventricular rate and calls it "Type II, 2:1 rhythm" which is quite erroneous.

One must wait for further evidence before interpreting Type aBB as a special form of intraventricular block. This interpretation is still less probable as applied to Type b_{1-3} , for we find that eight of the nine reported cases have a QRS duration which is normal. The possibility of disturbance of conduction in the terminal ramifications of the right bundle cannot be affirmed or denied since we know little of this condition in animals and nothing of it in man. Wilson and Herrmann,²⁰ on the bases of experiments with dogs, doubt that lesions of the terminal ramifications lead to substantial electrocardiographic changes.

2. *Theory of disturbed muscular balance.* This rests on the assumption that the mass of muscle which is cut off from the circulation by the closure of a vessel no longer gives rise to a process of electrical activity. This must lead to a change in the dynamic relation between the right and the left sides of the heart and to a distortion of the original ventricular complexes. It is easy to understand that an infarct of the left ventricle would lead not only to a decrease in the left axis deviation, but also to unusual modifications of the waves, for it is only a part of the left ventricle which is cut out; the potential of the remaining part is not disturbed. The fact that the appearance of the changes which we described in the initial complex was linked with a

large infarct supports this interpretation. It is more difficult to understand why in some cases the changes in the initial complex following coronary closure may be delayed considerably, and in a few cases they are reversible. We must remember that the development of necrosis is not always acute, nor is the process in the vessels always linked with the acute syndrome of coronary occlusion. Again there may be some return of circulation in the affected area either through a collateral circulation or through canalization, particularly when the general circulation improves with a rise of pressure in the aorta. The autopsy findings in the third group of cases fit in with this idea, for here the electrocardiogram showed simple decrease in the waves, while a double thrombosis had cut out a large part of the two sides of the heart. Our interpretation fits in with the opinion expressed by Hahn²¹ who in the case of a patient with a history of hypertension saw the axis deviation change from left to right after the second infarct, and who expressed the possibility that this was a result of change in the dynamic equilibrium following the infarct.

It would be pleasant to try to determine in the case of Type aBB and especially in the case of Type b_{1-3} how the electrical axis changes in the individual phases of the electrocardiogram with the appearance of changes in the initial complex. Apart from the fact that very recently serious objections have been raised to the older methods of determining axis deviation, our apparatus is, unfortunately, not set up to register two simultaneous tracings.

SUMMARY

Fifteen personal cases and 26 from the literature are reported, in which characteristic changes appeared in the initial complex following a coronary closure. These changes appeared immediately or some time after the insult, and remained definite or regressed.

The changes may be classed in three groups. In the first, one finds a modified form of left axis deviation with small R_1 and deep S_2 and S_3 . The characteristic of group two is the negativity of the principal deflection of all leads, whether this be S or Q. The third group is recognized by the shrinking of all the main waves while smaller deflections may persist unchanged.

The anatomical basis for the first two groups is an extensive necrosis of the anterior heart wall; for the third group it is necrosis of anterior and posterior walls as a result of two thromboses. Controlled by a series of 1,460 electrocardiograms chosen at random, these changes were found to be not pathognomonic, but most suggestive of the presence of infarct of the heart. They occur less frequently than do the hitherto recognized signs of coronary thrombosis, but they may be present in those cases in which there are no characteristic changes in the final complex.

As the interpretation of the QRS changes, a disturbance of the muscular balance of the two sides of the heart caused by the cutting out of a large mass of muscle is brought forward, but the possibility remains that for each group there is a localized disturbance of intraventricular conduction.

Later Note. While we were writing our paper, a work by Wilson, McLeod, Barker, Johnston and Klostermeyer (*Heart* 16: 155, June 1933) first came to our attention, at a time when our observations were already complete. These writers also studied changes in the QRS complex after coronary thrombosis and listed two types which they indicated as Type Q_1 and Type Q_3 . The first of these has in addition to Q_1 a very small R_1 and a deep S_2 and S_3 . Thus in Figs. 1, 2, 4 and 8 we recognize our Type aBB, in Figs. 2, 5 and 19 our Type b_{1-3} . Our third type is also shown twice, once with sure signs of intraventricular block, and once without this. The autopsy findings correspond to those of our cases. The authors place most emphasis on the Q changes but must add that the Q_1 type may occur without Q_1 as the single illustration evidences. The Q_3 type has nothing to do with the cases which we have described and at present seems to us not very characteristic. Concerning the relation between the electrocardiographic picture and the site and extent of the infarction, we feel that the authors are too cautious. Also they incline to the view that the changes in the initial complex are an expression of the cutting out of the infarcted part of the muscle.

REFERENCES

1. Herrick, J. B.: *J. A. M. A.* 81: 387, 1919.
2. Smith, F. M.: *Arch. Int. Med.* 22: 8, 1918.
3. Pardee, H. E. B.: *Arch. Int. Med.* 26: 244, 1920.
4. Wearn, J. T.: *Am. J. M. Sc.* 165: 250, 1923.
5. Wilson, W. J.: *Ann. Clin. Med.* 5: 238, 1926.
6. Fenichel and Kugell: *AM. HEART J.* 7: 235, 1931.
7. Oppenheimer and Rothschild: *J. A. M. A.* 69: 429, 1914.
8. Mahaim, I.: *Les maladies organiques du faisceau de His-Tawara*, Paris, 1931, Masson et Cie.
9. Edeiken and Wolferth: *AM. HEART J.* 7: 695, 1932.
10. Ziskin, T.: *Arch. Int. Med.* 50: 435, 1932.
11. Freundlich, I.: *Deutsches Arch. f. klin. Med.* 175: 129, 1933.
12. Levine, S. A.: *Coronary Thrombosis*, Baltimore, 1929, Williams & Wilkins.
13. Dressler: *Atlas der klinischen Elektrokardiographie*, Tafel VII, Abb. 22, Berlin and Wien, 1933, Urban & Schwarzenberg.
14. Condorelli, L.: *Die Ernährung des Herzens und die Folgen ihrer Störung*, Dresden, 1932, Theodor Steinkopff.
15. Smith, F. M.: *Arch. Int. Med.* 32: 503, 1923.
16. Oettinger, I.: *Ztschr. f. klin. Med.* 175: 129, 1933.
17. Cooksey and Freund: *AM. HEART J.* 6: 608, 1931.
18. Wennekebach and Winterberg: *Die unregelmässige Herztätigkeit*, Wien, 1927, p. 347, Wilhelm Engelmann.
19. Lewis, T.: *The Mechanism and Graphic Registration of the Heart Beat*, London, 1925, p. 182 ff., Shaw & Sons, Ltd.
20. Wilson, F. N., and Herrmann, G. R.: *Arch. Int. Med.* 26: 153, 1920.
21. Hahn, L.: *Ztschr. f. Kreislauf.* 25: 369, 1933.
22. Koch, Elsb.: *Ztschr. f. Kreislauf.* 25: 513, 1933.

THE DURATION OF THE QRS COMPLEX IN THE NORMAL AND IN THE ABNORMAL ELECTROCARDIOGRAM

A STUDY OF 500 CASES, WITH A NOTE ON NOMENCLATURE*†‡

SYLVESTER MCGINN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

A SURVEY of the literature has failed to reveal sufficient statistical data to establish durations for the QRS complexes of the normal human electrocardiogram at all ages, although 0.1 second as the upper limit has been set by common experience. The question has recently been asked whether or not this figure is higher than it should be. Hence we have made accurate measurements of the duration of the initial ventricular complexes in all leads in a series of 500 individuals, of whom 150 were normal and 350 had heart disease. In connection with this study several points of related interest have come to our attention.

LITERATURE

(a) *Normal Individuals.* A number of the standards employed in reading electrocardiograms originated in the earliest days of electrocardiography from the work of Lewis and Gilder⁸ which consisted of an analysis of the tracings of 52 normal males between the ages of eighteen and thirty-five years. The duration of the QRS complex was not considered at that time; but in a subsequent study by Lewis, among other determinations, the average duration of this complex for eight normal individuals was estimated to be 0.0784 second. In his book, *The Mechanism and Graphic Registration of the Heart Beat*, Lewis⁷ states in referring to the QRS group of deflections, "This group of deflections has a total duration of no more than 0.1 of a second, and usually constitutes less than one-third of the full ventricular complex." Again in another passage he says, "the QRS group of the normal human electrocardiogram lasts 0.08 of a second in the average." Ferguson and O'Connell² reported that in the electrocardiograms of 1,812 young men without symptoms referable to the heart only two had QRS durations of over 0.10 second. Jensen, Smith, and Cartwright⁴ found the duration of the QRS complexes to be between 0.06 and 0.08 second in a majority of 50 patients between the ages of fifty and sixty-five years.

*From the Cardiac Clinics and Electrocardiographic Laboratory of the Massachusetts General Hospital.

†Presented by title before the American Society for Clinical Investigation, Atlantic City, May 2, 1932.

‡The tables will be published in the reprints of this article. A copy of the reprint may be obtained by writing to the authors.

The electrocardiograms of normal children have been studied more extensively than those of adults. Seham¹⁰ in his section devoted to electrocardiography in Abt's *Pediatrics* gives the duration of the QRS complex as 0.036 second in normal infants eleven days to one year of age; 0.049 second in children one to five years of age; and 0.069 second in the later years of childhood. Lincoln and Nicolson⁹ found the average duration of the QRS complex to be 0.06 second as observed in the electrocardiograms of 222 normal school children between the ages of three and twelve years.

(b) *Patients With Heart Disease.* Lewis⁶ has reported measurements of the duration of the QRS complex in a few abnormal electrocardiograms. It was found to average 0.1005 in six curves with "left ventricular preponderance" and 0.0788 in six having right axis deviation consequent to mitral stenosis. He believed that the reasons for this difference are that there is a greater increase in the total muscle mass in left ventricular hypertrophy and that the end phases of the complex represent the spread of the waves in the left ventricular wall. Fahr¹ found that the QRS complexes of electrocardiograms of pure left ventricular enlargement were more prolonged than were those in normal curves and measured from 0.10 to 0.12 second. He attributed this prolongation to the increased length of the conduction path in the hypertrophied muscle through which the impulse must travel.

Wilson and Herrmann¹¹ have considered that a relationship exists between the duration of the QRS complex and the ventricular weight, but that when the measurement exceeds 0.10 second, some factor other than hypertrophy of the muscle is responsible, such as defects in the intraventricular conducting system.

PRESENT STUDY

We have studied a series of 500 electrocardiograms in which the QRS complexes of all three classical leads have been measured by means of the Lucas comparator. We have included in this series the tracings of 100 normal adults, 50 male and 50 female, and of 50 normal children twelve years of age and under. These individuals have been examined by us and have shown no evidence of cardiac disease. The remaining 350 electrocardiograms are representative of various cardiac disturbances and consist of 100 having abnormal left axis deviation, 50 of which have upright T-waves in Lead I, and 50 inverted T-waves in Lead I; 50 with abnormal right axis deviation; 50 with normal T-waves but from patients having heart disease, 50 with abnormal T-waves from patients having heart disease; 50 with intraventricular block of lesser grades; 30 with bundle-branch block, of which 20 show left axis deviation and 10 right axis deviation; and 20 cases of premature beats, of which 10 are of ventricular origin and 10 of auricular origin. The ectopic complexes show

right axis deviation in 5 of the electrocardiograms with ventricular premature beats and in the other 5 left axis deviation. Of the 10 tracings having auricular premature beats the abnormal P-waves are followed by normally shaped ventricular responses in 5 and by some degree of aberration of the ventricular responses in the other five.

Our procedure has been to measure three QRS complexes in each of the three leads by means of the Lucas comparator. The average duration of the complexes of each separate lead was estimated, and the largest of the three figures was taken as representing the maximum duration of the ventricular complex for that electrocardiogram. Simultaneous records in which Leads I and II and Leads III and I were taken together form a part of the total 500 tracings. All the electrocardiograms were standardized (one millivolt equals one centimeter) and none showing instrumental artefacts, such as overshooting, were included in the study.

The Lucas comparator has been described in detail by Lewis.⁵ It includes a microscope at each end of a movable bar, one of which is directed on the electrocardiogram and the other on a scale so graduated that readings are possible to one-hundredth of a millimeter. The computation of the measurements includes corrections for variance in the time marker by using percentages which automatically check themselves. The figures are translated into time relations so that the final answer as to the duration of the QRS complex is given in fractions of a second.

Lewis found that the possible error for this type of calculation in measuring R-R intervals was 0.0234 second for the maximum, but that the greatest variation more closely approached the minimum possible error of 0.0028 second. To insure as much accuracy as possible the measurements of 250 of our series of 500 electrocardiographic records were remeasured and compared with the first readings. The difference with very few exceptions amounted to only a few hundredths of a millimeter and depended upon the determination of the end points by two individuals.

FINDINGS

Normal Adults. The average duration of the QRS complex in the electrocardiograms of our series of 100 normal adults of all ages (see tables in reprints) was 0.0777 second. Half this group of patients were males who had an average duration of the QRS deflection of 0.0833 second; 66 per cent of these males had a QRS duration longer than 0.0800 second. The 50 females had shorter duration times of the QRS complex than did the males. The average for this group was 0.0722 second with only 20 per cent over 0.0800 second. The width of the QRS waves had no consistent relationship to the ages of these 100 normal adults, to their pulse rates, or to the amplitudes of their ventricular complexes. Of the 50 normal male patients 11 were tall in stature, 10

of whom had QRS complexes wider than 0.0833 second, the average for the group. One tall patient was included in the group of 50 normal females, and she had a duration time of 0.0782 second. The widths of the QRS complexes in patients considered to be overweight were below the average for the group as frequently as they were above it.

The longest QRS times were most frequently observed in Lead III; this was true in 44 tracings. The duration of the QRS complex was the most prolonged in Lead II in 37 electrocardiograms and in Lead I in 19 instances. In the electrocardiograms of 16 of the normal adults, Leads I and II and Leads III and I were taken simultaneously; the widest QRS wave was found in Lead III in 9 of these individuals.

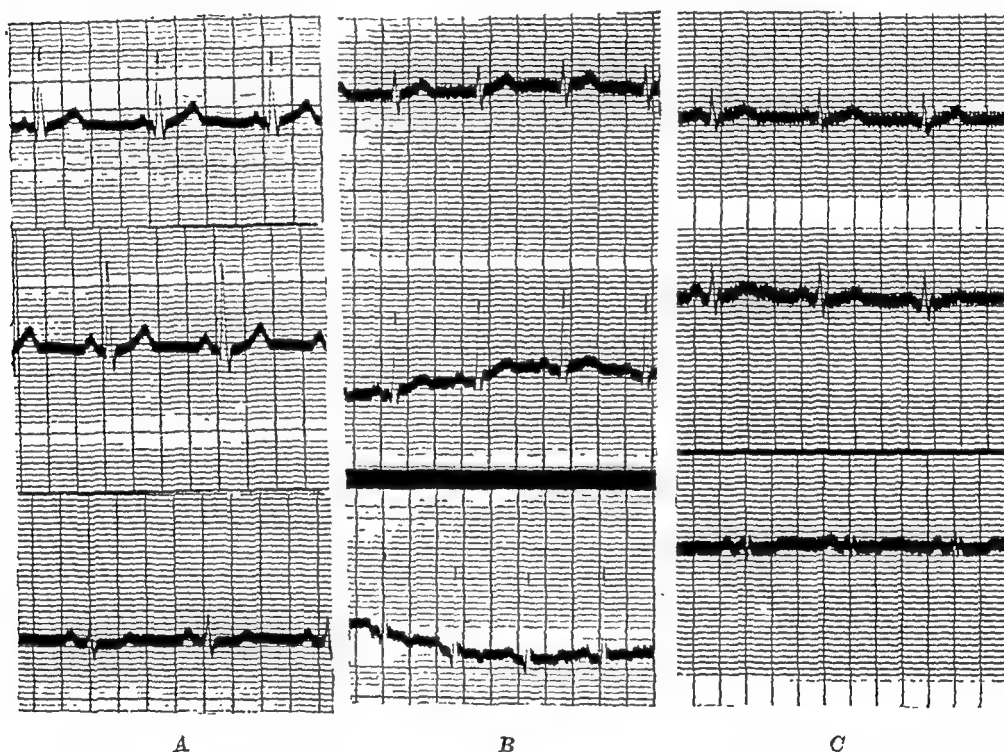


Fig. 1.—Electrocardiograms of normal individuals. A, Common type with the usual QRS complex; B, widening of the QRS in Lead III due to an upright S-wave (Leads I and II recorded simultaneously); C, widening of the QRS due to notching in Leads II and III (Leads I and II recorded simultaneously); the voltage of the QRS waves in this record is rather low.

Leads I, II, and III are shown in order in these records and in those of the figures to follow. Time interval 0.2 second. Amplitude 1 mm. 10^{-4} volt.

In 18 of the 100 normal adults' electrocardiograms the QRS duration was more than 0.0900 second. The majority of these records showed individual variations in the ventricular complexes that accounted for the prolongation. Slurring of the descending limb of the R-wave and notching of the QRS in Lead III were found frequently. Three of these 18 tracings had a duration of the QRS wave greater than 0.100 second; 2 of these 3 had in Lead III low voltage and considerable notching of the ventricular complexes. An "upright S-wave" superimposed on the descending limb of the R-wave in Lead III was found in three

tracings and an "upright Q-wave" was found interrupting the ascending phase of the R-wave in Lead I in another electrocardiogram.

Normal Children. The electrocardiograms of 50 normal children twelve years of age and under were studied to determine the duration of the QRS complex in childhood. It was found to average 0.0719 second, very closely approximating the average measurement found in the 50 normal females and somewhat longer than has been previously reported for children. There were 26 boys and 24 girls in this series, the former tending to have slightly wider QRS complexes than the latter. Of 28 cases in which the duration of the ventricular complex was more than 0.0700 second, 18 were boys. The youngest children were included in the group whose tracings showed the QRS duration to be 0.0700 second or less, the average age being 7.4 years as compared with 8.3 years for the group with QRS durations longer than 0.0700 second. The ages of the children were as follows: two years 4 children, three years 1, four years 1, five years 2, six years 8, seven years 4, eight years 5, nine years 7, ten years 7, eleven years 6, and twelve years 5.

ABNORMAL CASES

Abnormal Left and Right Axis Deviation. The duration of the QRS complex was determined in 100 electrocardiograms having an abnormal degree of left axis deviation; 50 of these had upright T-waves in Lead I and the other 50 inverted T-waves in Lead I. In the 50 cases with upright T-waves in Lead I the QRS wave had an average duration of 0.0889 second; Lead III was completely inverted in 14 of these cases (in 8 of these the QRS wave duration exceeded the average for the group of 50). The electrocardiograms of this first group of 50 cases were obtained from 30 males and 20 females; of the latter only 4 had QRS complex durations greater than the general average of 0.0889 second for the 50 cases. The maximum duration of the ventricular complex was found in Lead III 19 times, in Lead II 17 times, and in Lead I 14 times. There were 36 tracings with simultaneous records of Leads I and II and of Leads III and I. In these special films the QRS complex was widest in Lead III fifteen times and in Leads II and I twelve and nine times respectively.

The average duration of the QRS wave in the 50 cases having an abnormal degree of left axis deviation and an inverted T-wave in Lead I was 0.0985 second. Lead III was completely inverted in 6 of these 50 electrocardiograms, of which number 2 had QRS waves wider than the average for the group. There were tracings from 36 male patients and 14 female patients. Nine of the female patients had QRS waves wider than 0.0985 second which was the average for these 50 patients. The widest QRS wave was recorded in Lead III in 21 instances, in Lead II in 11, and in Lead I in 18. There were 20 electrocardiograms in

which two leads were taken simultaneously, and it was shown that the widest QRS wave appeared seven times in Leads II and III respectively and 6 times in Lead I.

Fifty electrocardiograms having an abnormal degree of right axis deviation were measured, and in these the average duration of the QRS complex was found to be 0.0870 second. Equal numbers of males and females were represented in this series and were evenly distributed in relation to the average duration of the QRS wave for the group. The widest QRS complex was found 23 times each in Leads II and III and only 4 times in Lead I. In 13 electrocardiograms with leads taken simultaneously, the greatest duration of the QRS complex was found in Lead

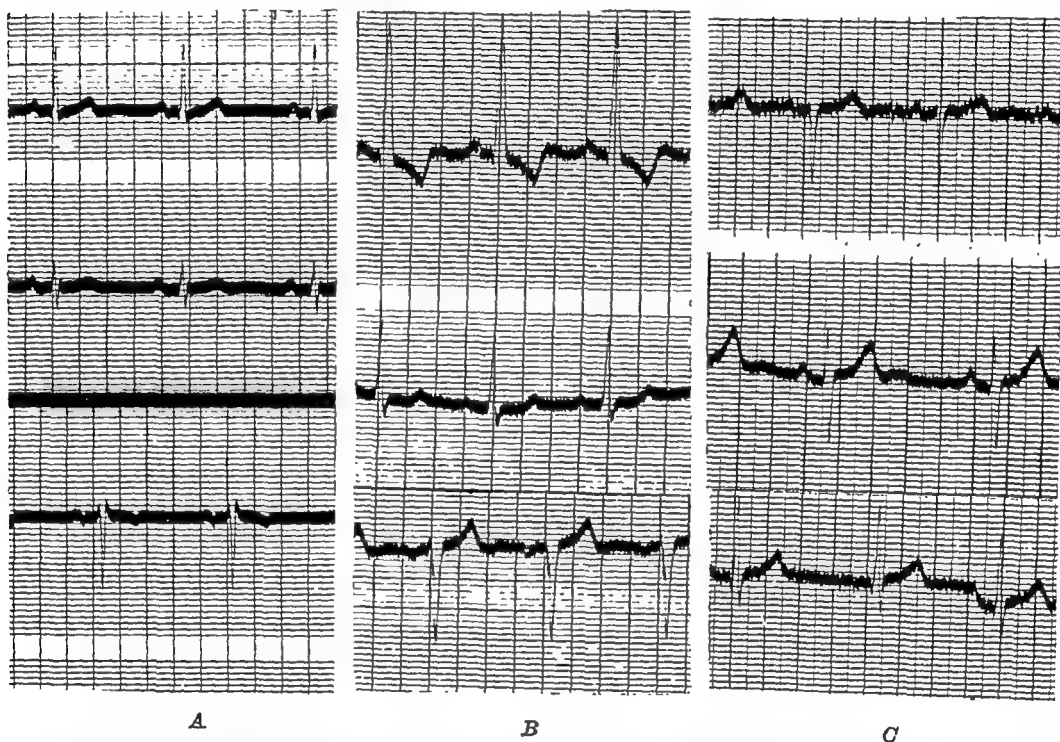


Fig. 2.—Electrocardiograms with abnormal axis deviation. *A*, Left axis deviation with upright T-wave in Lead I (Leads I and II recorded simultaneously); *B*, left axis deviation with inverted T-wave in Lead I (Leads I and II recorded simultaneously); *C*, right axis deviation.

III five times, in Lead II six times, and in Lead I twice. Eleven of the patients whose electrocardiograms showed an abnormal degree of right axis deviation had congenital heart disease and the others, with two exceptions, had mitral stenosis. Nine of the patients with congenital heart disease had QRS complexes wider than 0.0800 second.

A comparison of the above three groups of electrocardiograms (each group containing 50 electrocardiograms) indicates that the average duration of the QRS complex is longest in the records having abnormal left axis deviation with inverted T-waves in Lead I. The average durations of the QRS waves in those tracings having abnormal left axis deviation with upright T-waves in Lead I and

those with abnormal right axis deviation were similar, and more closely approached that found for normal adults although still exceeding it somewhat.

Electrocardiograms of 100 Patients With Heart Disease Without Any Abnormal Degree of Either Left or Right Axis Deviation. The electrocardiograms of 100 patients with heart disease without any abnormal degree of either left or right axis deviation were studied, and the duration of their QRS complexes was determined. There was no bundle-branch block in these tracings. In 50 of the 100 cases there were abnormal T-waves in Lead I or Lead II, and in 50 there were no abnormal T-waves in either Lead I or Lead II.

All the 50 electrocardiograms in which the T-wave was upright in Leads I and II were those of patients in whom we had made the diagnosis of undoubted angina pectoris, 42 of their number being males. The average duration of the QRS complexes in these 50 cases was 0.0779 second. Twenty-two of the 50 records showed the widest QRS complexes in Lead II, 17 in Lead III, and 11 in Lead I. Four of the 7 films in which the leads were taken simultaneously showed the widest QRS complexes in Lead I.

The average duration of the QRS complex was 0.0827 second in the 50 electrocardiograms of patients having heart disease and abnormal T-waves in Lead I, in Lead II, or in both Leads I and II, but in which there was neither abnormal axis deviation nor bundle-branch block. The diagnosis of coronary thrombosis was made by us clinically in all these 50 patients. There were 21 tracings with an inverted T-wave in Lead I and 14 with a diphasic T-wave in Lead I. Of the remaining 15 electrocardiograms 10 had an inversion of the T-wave in Lead II and 5 had diphasic T-waves in Lead II. Six of the 10 electrocardiograms having inverted T-waves in Lead II had QRS wave durations of over 0.0900 second; otherwise there was no suggestive relationship between the width of the QRS complex and the type of T-wave. Forty-four of these 50 electrocardiograms were from male patients. The widest QRS complexes were found 21 times each in Leads I and II. There were 17 tracings in which two leads were taken simultaneously, and of this number the QRS wave was widest in Lead II in the majority of instances.

Intraventricular Block Including Full Bundle-Branch Block. The ventricular complexes were studied in 50 electrocardiograms showing the presence of intraventricular block of slight to moderate degrees (not the full classical bundle-branch block) and in 30 electrocardiograms showing full bundle-branch block. The average duration of the QRS waves in the first group was 0.1307 second with the two extremes 0.1007 second and 0.1640 second. There were 46 males and 4 females represented in this group of 50 patients; two of the 50 patients complained of diseases not related to the heart, two had functional cardiac dis-

turbances,* and the remainder had complaints due to organic heart disease. The widest QRS complex was found in Lead III in 19 tracings, in Lead II in 18, and in Lead I in 13. Of 10 electrocardiograms with two leads taken simultaneously, the duration of the QRS complex was greatest in Lead III on 6 occasions.

Three additional electrocardiograms were measured in which the interpretation had been intraventricular block on account of the shapes of the QRS waves, although the duration of the ventricular complex was less than 0.100 second. The measurements of the durations of the QRS waves in these cases were 0.0896 second, 0.0931 second, and 0.0996 second respectively. It is thought that the interpretation of intraventricu-

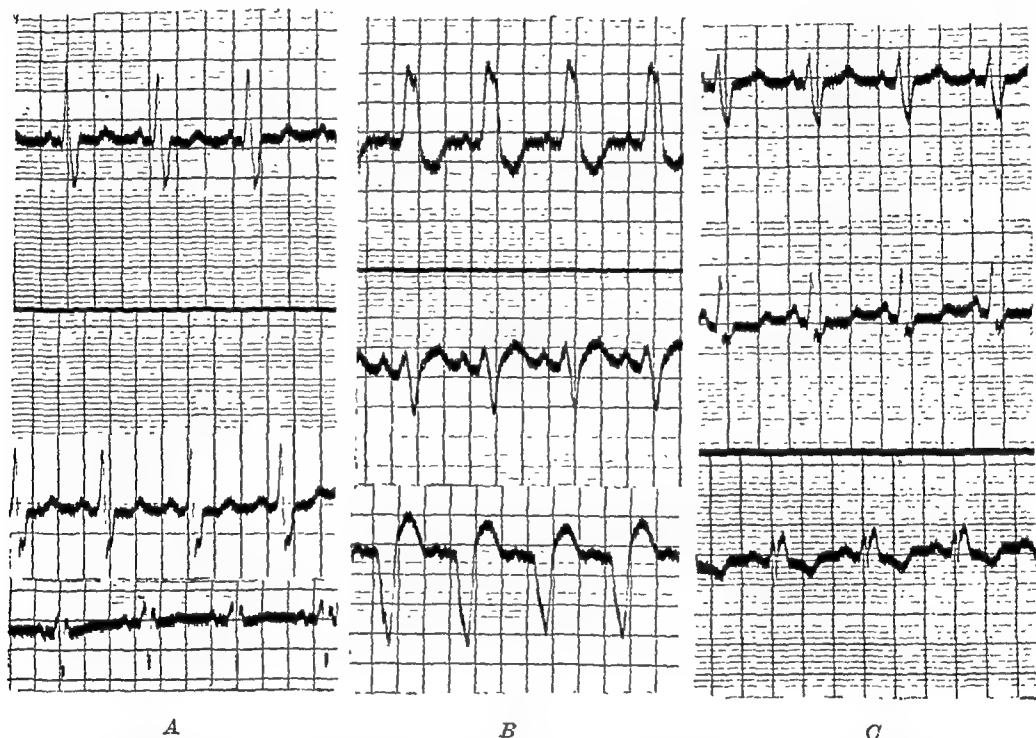


Fig. 3.—Electrocardiograms showing defects in the ventricular conducting system. A, Intraventricular block of lesser degree; B, bundle-branch block with left axis deviation; C, bundle-branch block with right axis deviation (Leads I and II recorded simultaneously).

lar block was justified because of the extreme notching and altered shape of the ventricular complexes despite their relatively short durations.

The durations of the ventricular complexes were estimated in 30 electrocardiograms having typical bundle-branch block, of which number 20 had left axis deviation and 10 right axis deviation. The former under the old terminology are considered to indicate defects in the

*An electrocardiogram was studied representative of the group of cases reported by Wolff, Parkinson, and White¹² in which there were sometimes widened QRS waves with short PR intervals and at other times normal complexes with PR intervals of usual length. Two complexes of each type were measured, and the intervals from the beginnings of the P-waves to the ends of the S-waves were found to be approximately the same (0.22 second and 0.21 second respectively). This is evidence supporting the suggestion by Holzmann and Scherf³ that in these cases there may be a special conduction tract between auricles and one or the other ventricle in addition to the A-V node and the bundle of His.

right branch of the bundle, but left bundle-branch block according to the new nomenclature. Lewis found that the average duration of the QRS complex in 7 tracings having such changes was 0.1396 second; in our 20 cases it was 0.1499 second. Twelve of the 20 patients were males. The majority of these 20 records showed the widest QRS waves in Lead II.

The 10 tracings having bundle-branch block with right axis deviation gave an average duration of the QRS complex of 0.1412 second. Six of these patients were males. The widest QRS complexes were most often found in Lead III in this group.

Ventricular and Auricular Premature Beats. Twenty electrocardiograms having frequent premature beats were studied, and the durations of the first ventricular complexes (QRS waves) were determined. It was not possible to obtain 3 of these special complexes in every lead for measurement as had been the procedure throughout the series; however, no fewer than 7 premature beats were measured in each instance.

The average duration of the QRS waves of ventricular premature beats with left axis deviation was 0.1374 second in 5 electrocardiograms. Three of these patients were males. The duration of the QRS waves of ventricular premature beats having right axis deviation was 0.1401 second in 5 electrocardiograms of 5 other cases. Those ventricular complexes having the longest time intervals were found most frequently in Lead III.

The normal ventricular responses to auricular premature beats were measured in 5 electrocardiograms, and the average width of the QRS waves was found to be 0.0801 second. There were four males and one female represented by these electrocardiograms. The widest QRS complexes were found twice in Lead II and twice in Lead III. In five other electrocardiograms the duration of the QRS wave was determined for aberrant ventricular responses to auricular premature beats. The average duration of these QRS intervals was 0.1216 second. Three of the tracings were from male patients. The greatest aberration of the ventricular responses to ectopic auricular beats was observed twice in Lead I and twice in Lead II.

NOTE ON NOMENCLATURE

The present study has called our attention to the inconsistencies of the nomenclature of the QRS complex of the electrocardiogram. In describing the ventricular complex the method most in vogue at the present time of calling the upward deflection of the QRS complex the R-wave and the downward deflections Q and S according as they precede or follow the R-wave is unsatisfactory in that there may be more than one upward deflection (see Lead III of Fig. 4A) and in that the first downward deflection may be deep and wide, not in appearance like the usual

Q-wave and in time coincident with the R-wave of Leads I and II (see Lead III of Fig. 4B). Nor is the earlier nomenclature of Einthoven wholly satisfactory, even though it is more consistent in that the deflections are labelled according to their timing in the cardiac cycle and not merely arbitrarily; that is, Q-, R-, and S-waves may be upright or inverted but represent in sequence phases of the first spread of the excitation wave into the ventricles; thus in Lead III of Fig. 4A there are in sequence an upright Q-wave, an inverted R-wave, and an upright S-wave.

The timing, however, of the individual deflections is often difficult or

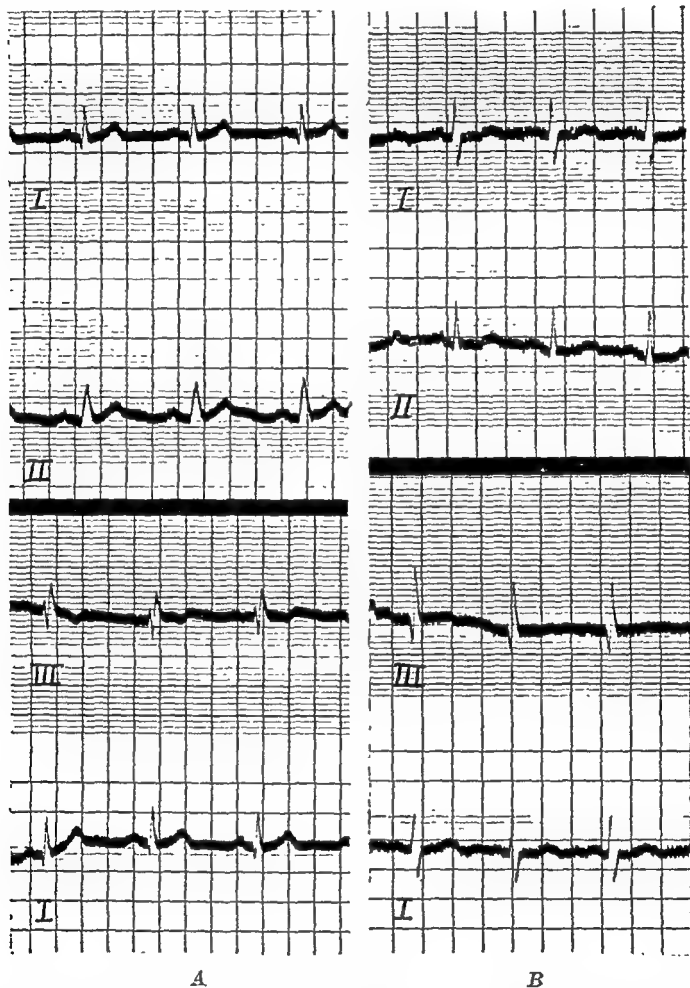


Fig. 4.—Electrocardiograms showing variations of QRS complexes, with Leads I and II taken simultaneously, and Leads III and I taken simultaneously. A, The QRS in Lead III presents two upright peaks and one directed downward, the downward deflection corresponding in time with the upright R in Lead I. It represents an inverted QRS complex; B, the QRS in Lead III is diphasic, the first deflection being downward and followed by an upward deflection. Timing of the complexes shows that the downward deflections in Lead III occur simultaneously with the upright peaks or R-waves in Lead I.

impossible, when we are dealing with a diphasic or monophasic curve, unless two or more leads are recorded simultaneously. As a matter of fact, the old German designation for the QRS wave, namely I standing for Initialschwankung, is in some respects preferable to QRS. But either designation is suitable if we limit ourselves to a clear, simple description

of what we actually see— thus the QRS wave may be described as consisting of plus and minus deflections extending so many millimeters above or below the baseline without any arbitrary and often misleading attempt to label the individual deflections by exact letter; in Fig. 4A the QRS wave in Lead III may be briefly and accurately presented as QRS equals plus 1, minus 2, plus 4, and in Fig. 4B QRS₃ equals minus 3, plus 7. For the past five years or more we have used successfully at the Massachusetts General Hospital this method of describing the QRS complexes in electrocardiograms showing low voltage in all leads. The method may usefully be expanded to include all electrocardiograms. Finally, the duration of the individual deflections may be expressed either roughly or accurately by measurement in addition to their direction and amplitude. In the last analysis, however, a reproduction of the complex itself by photograph, tracing, paper, or rough drawing is more instructive than any amount of description, more or less as actual sight of a patient is more valuable than a word picture, no matter how good it is.

SUMMARY

1. Three ventricular complexes have been measured with the Lucas comparator in each of the three leads of 500 human electrocardiograms (150 normal subjects and 350 abnormal subjects) in order to determine the average duration of the QRS waves.

2. The average duration of the QRS complex in 100 normal adults was 0.0777 second. Fifty of the patients were males with an average duration of the QRS time interval of 0.0833 second, and 50 were females with a shorter time interval of 0.0722 second. The average duration of the QRS complex in 50 normal children twelve years of age and under was 0.0719 second with the males having slightly longer duration times. Some particular variation of the ventricular complex such as notching or upright S- or Q-waves accounted for QRS waves wider than 0.0900 second.

3. The only important correlation of the duration of the QRS wave in normal individuals is apparently that with heart size; the taller the person, as a rule, the wider the QRS complex. Neither the age of the patient nor the cardiac rate appeared to have any relationship to the duration of the QRS wave except that the QRS waves of children are in general narrower than are those of adults. The QRS wave was found to be widest most frequently in Lead III.

4. The normal upper limit of duration of the QRS wave of the electrocardiogram in children of twelve years and under may be accepted as 0.09 second, and in adults as 0.10 second. In our series of 50 normal children only 2 showed QRS waves more than 0.09 second long (0.0915 and 0.0992) and in our series of 100 normal adults only 3 showed QRS waves over 0.1 second in duration (0.1006, 0.1017, and 0.1053).

5. In 50 electrocardiograms having an abnormal degree of left axis deviation and an upright T-wave in Lead I the average QRS wave duration was 0.0889 second, and in 50 tracings with an abnormal degree of left axis deviation associated with an inverted T-wave in Lead I the duration time averaged 0.0985 second. The duration time of 0.0870 for the QRS waves in 50 electrocardiograms having an abnormal degree of right axis deviation was thus slightly shorter than that of the cases with an abnormal degree of left axis deviation.

6. The QRS wave durations of 100 electrocardiograms of patients having heart disease without bundle-branch block or an abnormal degree of axis deviation were measured. The average duration of the QRS complex was 0.0779 second in 50 patients having angina pectoris without abnormal T-waves in Lead I or Lead II. The average duration was 0.0827 second for 50 patients who had had coronary thrombosis and showed abnormal T-waves in either Lead I or Lead II.

7. Fifty electrocardiograms interpreted by us as showing intraventricular block of lesser degrees had an average QRS wave duration of 0.1307 second. The average duration of the ventricular complexes was 0.1499 second in the 20 cases of full bundle-branch block with left axis deviation and 0.1412 second in 10 cases of full bundle-branch block with right axis deviation.

8. The average duration of the QRS complexes of 5 ventricular premature beats with left axis deviation was 0.1374 second and of 5 ventricular premature beats with right axis deviation 0.1401 second. The QRS interval averaged 0.0801 second in duration for the normal ventricular responses to premature beats of auricular origin in 5 cases, and 0.1216 second for aberrant ventricular responses to auricular premature beats in 5 other cases.

9. This study has called our attention to the inconsistencies of our present nomenclature of the deflections of the QRS complex. We suggest that a more satisfactory method of describing this complex would be to state positive and negative deflections by appropriate signs with amplitudes expressed in millimeters; thus, QRS equals minus 2, plus 12, minus 5. The duration of the total complex or of the individual deflections may be added if abnormal.

REFERENCES

1. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch. Int. Med.* 25: 146, 1920.
2. Ferguson, D., and O'Connell, J. T.: Cardiovascular Observations Including a Series of Electrocardiograms of 1812 Men Without Heart Symptoms, *U. S. Naval Med. Bull.* 24: 860, 1926.
3. Holzmänn, M., and Scherf, D.: Über Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr. f. klin. med.* 121: 404, 1932.
4. Jensen, J., Smith, M., and Cartwright, E. D.: The Electrocardiogram in Late Middle Life, *AM. HEART J.* 7: 718, 1932.

5. Lewis, T.: Electrocardiographic Plate Studied by Means of the Comparator, *Heart* 7: 117, 1919.
6. Ibid.: The Spread of the Excitatory Process in the Vertebrate Heart. The Human Ventricle, *Phil. Trans. Roy. Soc.* 207: 284, 1916.
7. Ibid.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, ed. 3, pp. 45 and 128, Shaw and Sons, Ltd.
8. Lewis, T., and Gilder, M. D. D.: The Human Electrocardiogram: a Preliminary Investigation of Young Male Adults to Form a Basis for Pathological Study, *Phil. Trans. Roy. Soc.* 202: 351, 1912.
9. Lincoln, E. M., and Nicolson, G. H. B.: The Hearts of Normal Children. Electrocardiographic Records, *Am. J. Dis. Child.* 35: 1001, 1928.
10. Seham, M.: *Abt's Pediatrics*, Philadelphia, and London, IV, 298, 1924, W. B. Saunders Co.
11. Wilson, F. N., and Herrmann, G. R.: Relation of QRS-Interval to Ventricular Weight, *Heart* 15: 135, 1930.
12. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia. *AM. HEART J.* 5: 685, 1930.

DYNAMIC DILATATION OF THE THORACIC AORTA*

W. K. PURKS, M.D.

BOSTON, MASS.

IN ONE sense of the word all dilatation of the aorta is dynamic dilatation, for without the pressure of the blood within the vessel dilatation would not occur. The term "dynamic dilatation" as commonly used, however, indicates that the internal pressure of the blood is the sole cause of the dilatation and that structurally the aorta is normal and consequently after death returns to normal size. In view of the marked elasticity of the normal aorta which year after year must yield to the impact of the systolic thrust of the heart it seems remarkable that so-called dynamic dilatation does not occur more often. Considered on a purely physical basis, if an individual's diastolic pressure changes from 80 mm. Hg to 120 mm. Hg, his aorta must be distorted to some extent. The distortion may be chiefly manifest as tortuosity or as an increase in width, the tortuosity being due to an increase in length. It is at times important to know whether the dilatation of the thoracic aorta seen by x-ray examination is functional (dynamic) or represents a diseased aorta. Our attention was recently focused on this question by seeing a patient in whom the roentgenologist found an aorta dilated to aneurysmal proportions and in whom the pathologist found an aorta of normal size.

CASE REPORT

E. M. Medical Case No. 42513. A negro chef, aged forty-five years, was admitted to the hospital Feb. 8, 1933, complaining of precordial pain and shortness of breath of three months' duration. His family history was negative. There was no history of syphilis, though he had had gonorrhea twelve years previously. During the last two years he had been troubled by frequent occipital headaches. Three months before admission he first noticed precordial pain. It was persistent though of variable intensity and was accentuated by exertion, at which time it became quite severe. He had frequent paroxysms of nocturnal dyspnea. For two months there had been frequent attacks of temporary blindness in the right eye followed by diplopia.

Physical Examination.—Showed good development and nutrition. He was in moderate respiratory distress. Both optic discs showed a swelling of one diopter. A few white spots were seen in both retinas. There was evidence of vascular disease and one small hemorrhage on the right. The carotid arteries pulsated forcefully. There was no tracheal tug. The lungs showed occasional coarse râles at the right base. The cardiac impulse was 12 cm. to the left of the midline. The left border of cardiac dullness measured 12.5 cm., right border of cardiac dullness 4 cm. from the midline and the supracardiac dullness 6 cm. A systolic murmur was

*From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.

heard at the apex. There was no diastolic murmur. The heart action was regular. The aortic second sound was ringing in character. The blood pressure was 200 mm. systolic and 160 diastolic. The remainder of the examination was not remarkable.

His admission temperature was 99°, pulse 80 and respirations 24. The red blood count was 4,600,000, hemoglobin 82 per cent (S), white blood count 7,500 with a normal differential. The blood Wassermann and Hinton tests were positive. An x-ray picture of the heart showed a widening of the aorta in the anterior, posterior and lateral views.

He had repeated attacks of severe precordial pain, partially relieved by nitroglycerin. On one occasion he had severe pain localized in the epigastrium, associated with a fall of blood pressure to 150/100 and with electrocardiograms quite typical of coronary occlusion. There was no fever, leucocytosis or pericardial friction rub. His blood pressure rose after the attack to 225/135. He continued, however, to have repeated attacks of precordial pain, frequently was covered with sweat, and was extremely weak. Finally on the forty-sixth day in the hospital he had a severe attack and died. Some gastrointestinal symptoms and findings were present but were not pertinent to the present consideration of the case. He was thought to have hypertension, chronic myocarditis and coronary occlusion plus a syphilitic aortitis with aneurysm.

At autopsy surprisingly enough there was neither a dilated aorta nor a coronary occlusion. The aorta measured 7 cm. in circumference just above the valves, and just proximal to the right innominate artery 6.5 cm. in circumference. Its elasticity was extremely well preserved. The proximal aorta was essentially negative, except for a few small atheromatous patches. The heart was greatly enlarged, weighing 520 gm. There were no valve lesions. There were no areas of myocardial fibrosis or softening. There was a generalized mottling with alternating areas of reddish brown and pale brown colors. There was myocardial hypertrophy most marked in the left ventricle. The coronaries were of large caliber, patent throughout and grossly showed little evidence of disease. Other features of the gross pathology need not be described in detail. Suffice it to say, there was a chronic progressive vascular nephritis, acute hemorrhagic colitis, hypoplasia of the thyroid, mesenteric lymphadenitis, pleural adhesions and phleboliths in the prostatic venous plexus. The most significant feature of the microscopic study was the remarkable character of the vascular lesions. Vessels of the various tissues showed essentially the same picture. There was marked degeneration of the intima and media of small arterioles to medium-sized and small arteries. There was in addition to the degeneration an inflammatory cell infiltration and a hyperplastic response. Some vessels showed hyalinization of the media with early evidence of degeneration. These lesions were not diagnostic of a syphilitic peripheral arteritis though suggestive. A detailed consideration of these remarkable lesions is not the province of the present study. Microscopically the aorta showed some thickening of the intima with some degenerative changes. There was a slight bluish stain throughout the media. The structural relations were, however, well maintained. There was no evidence of syphilis. Elastic tissue stains showed an abundance of normal elastic tissue.

This patient did not have a perfectly normal aorta and there was a history of syphilis. He is nevertheless presented as a case of dynamic dilatation because the slight pathological lesions found at autopsy were in an aorta of normal size and yet there was unquestionable dilatation before death. An explanation of the electrocardiographic changes is not essential to the present report. It seems highly probable, however,

that even in the absence of a major focal coronary thrombosis there was such marked disease of the small vessels as to produce a widespread anoxemia of the heart muscle which would alter the electrocardiographic picture.

How can this case be explained and how often does the aorta dilate to abnormal proportions because of pressure changes? The literature contains relatively few references to dynamic dilatation. Some authors feel, as does Wilson,¹ that "It is doubtful if a state of so-called dynamic dilatation ever occurs in a perfectly normal aorta no matter what the blood pressure is." Bayley² has recently studied the subject and finds that the conditions in which dynamic dilatation is most often described are aortic insufficiency of rheumatic origin, chronic nephritis with hypertension, hyperthyroidism and cardiac neurosis. He reports three cases in which a dilatation of the thoracic aorta demonstrated by x-ray examination was considered as "dynamic" because organic causes such as syphilis and arteriosclerosis were not present. To the above mentioned conditions in which dynamic dilatation is likely to occur we would add stenosis of the aorta, especially that form of congenital stenosis of the aorta found with coarctation of the aorta.

From the case records of the Peter Bent Brigham Hospital we have studied the x-ray and clinical features of a number of cases in which dynamic dilatation seemed likely to occur. These will be considered in five groups. In considering the whole problem the question at once arises as to just what are the upper limits of measurements for the normal aorta. The limits, of course, vary widely at different ages, and in the last analysis the general impression of the roentgenologist of a given case is probably of more value than are actual measurements compared with a theoretical normal. Our interpretation of whether or not a given aorta is dilated may not conform to the criteria of others, but throughout the study the same criteria have been used and findings in the different groups are comparable. We have considered an aorta dilated when in fluoroscopy it appeared definitely so in the oblique view or when the transverse measurement in the posteroanterior view of the 7-foot plate exceeds 6 cm. Measurements in the oblique view were not often available. In none of these patients was dilatation of the aorta sufficient to produce the murmur of aortic insufficiency; in the group of aortic insufficiency of rheumatic origin there was an aortic insufficiency of organic valve origin.

GROUP I. AORTIC INSUFFICIENCY OF RHEUMATIC ORIGIN

In this group of 39 patients all were under thirty years of age. The average age was 19.1 years. This factor largely eliminates arteriosclerosis as a cause of aortic disease. We may assume that arteriosclero-

sis sufficient to cause gross alteration in aortic contour rarely occurs before the age of forty years. In this group, as in each of the others, all cases in which there was any suggestion of syphilis have been excluded. The average systolic blood pressure, as seen in Table I, was 129.6 mm. Hg, the average diastolic pressure 44.9 mm. Hg, and the average pulse pressure 84.9 mm. Hg. Dilatation of the aorta was recorded in 25.6 per cent, and the aorta was described as tortuous in 2.5 per cent. An effort to compare these figures with those of other observers shows that such studies have not been frequently done. Vaquez and Bordet,³ in one of the best early books on roentgenography of the heart, state that in aortic insufficiency there is a dilatation of the aorta at its origin from the valvular ring to the level of the arch where it resumes its normal caliber. Wiggers⁴ refers to an increase in the aortic shadow in aortic insufficiency. White⁵ states that the active oscillations of pressure associated with aortic insufficiency may give rise to very marked pulsation in the aorta with considerable dilatation and prominence of the aorta during systole but with a collapse to *nearly* normal caliber during diastole. Bayley² found dilatation of the aorta in 8.4 per cent of his cases. Scott⁶ mentions the *frequent* occurrence of dilatation in aortic insufficiency, especially in cases where there is a high systolic pressure and a low diastolic pressure. Holmes,⁷ on the other hand, found a normal aortic shadow in all of 15 cases. There is then a rather wide variation of opinion.

In those cases of our series showing dilatation the average systolic blood pressure was 145.2 mm. Hg, the average diastolic pressure 40.6 mm. Hg, and the average pulse pressure 104.6 mm. Hg. That is to say, those with dilatation in contrast to those without dilatation of the aorta had a considerably higher systolic and pulse pressure and about the same diastolic pressure. Clearly then there was much more tension on those that showed dilatation. Were these aortas diseased also? Many observers have described lesions of the aorta as a result of rheumatic fever. These have chiefly been acute processes. Sir Clifford Albutt⁸ states that the dilatation which occurs in rheumatic and other forms of aortitis than syphilitic usually subsides as the disease becomes inactive. Our patients were not in the acute phase of the disease. Deutsch⁹ has emphasized that aortic disease due to rheumatic fever and other infections is not uncommon. Unfortunately, we do not have autopsy material in the present series and cannot say with certainty that no disease was present in the aorta. Certainly, however, our general experience indicates that in young people coming to necropsy with rheumatic heart disease demonstrable structural disease of the aorta is not often found. Functionally the aorta may be impaired.

GROUP II. HYPERTENSION AND CHRONIC NEPHRITIS WITH HYPERTENSION

In this group there were 21 patients with an average age of 25.5 years. All were under thirty-five years of age. The average systolic pressure was 202.4 mm. Hg, the average diastolic pressure 130.9 mm. Hg, and the average pulse pressure 72.4 mm. Hg. In 42.8 per cent the aorta was dilated, and in 14.6 per cent it was described as tortuous. Here again we find that there are few comparable studies in the literature. Albutt quotes Hart's¹⁰ description of plethoric people whose heart is both enlarged and dilated and whose aorta displays marked distensibility and increased capacity, though it is normal and the increased capacity is not at the expense of loss of resiliency. Sheldon¹¹ reported marked dilatation of the aorta by x-ray examination in a boy aged ten and a half years who had chronic nephritis and a blood pressure of 210/155 mm. Hg. Post-mortem study showed the aorta entirely normal in size. He regarded the dilatation as a direct mechanical consequence of the increased pressure, the increased pressure being maintained throughout diastole. Evans¹² in a study of arteriosclerosis in children reports one case that had such dilatation of the aorta as to produce pulsation suggesting aneurysm. No x-ray films were taken. The boy, aged fourteen years, had chronic nephritis and a blood pressure of 260/200 mm. Hg. At autopsy the aorta was not dilated. In 14 cases of chronic nephritis and hypertension in adults Smith and Kilgore¹³ found x-ray evidence of a dilated aorta in all but 3 cases. They considered the upper limits of normal as 4.5 to 5.5 cm. and classed as dilated all cases with transverse measurements exceeding 6 cm. Contrary to what one might have expected, those patients showing measurements of 7 to 9 cm. were younger than those with measurements of 6 to 7 cm. This quite naturally suggested to them that when hypertension supervenes on an aorta already somewhat stiffened by age, it does not stretch as easily as a younger one would. Autopsies were not done in their series. Holmes⁷ states that diffuse dilatation of the aorta is not an unusual finding in hypertension, and White⁵ mentions the fact that some of the dilatation seen by the roentgen examination in hypertension is not found at post-mortem since it is temporary and depends upon the intra-aortic hydrodynamic state. Strangely enough although Wilson¹ did not find at autopsy the degree of dilatation evidenced on the x-ray screen in 2 of his cases of hypertension, yet he concluded that dynamic dilatation does not occur.

In regard to the present series the assumption seems justified that the dilatation which was demonstrated was due to the pressure alone because other reasonable causes were not present. We cannot say whether or not the persistent high tension may have exceeded the elastic limit of the aorta and resulted in real dilatation which could have been

demonstrated at autopsy. Even if such had been the case, the aorta probably would have appeared structurally normal under the microscope. Functionally it would not be normal.

GROUP III. HYPERTHYROIDISM

This group is small. It consists of 26 patients, none of whom was over forty years of age. The average age was 29.6 years, the average systolic blood pressure 133 mm. Hg, the average diastolic pressure 64.4 mm. Hg, and the average pulse pressure 68.1 mm. Hg. The average increase in metabolic rate was +58 per cent. Only 4 cases, 15.3 per cent, showed a dilated aorta and none of the aortas was described as tortuous. Bayley² found dilatation in 12.1 per cent of 263 cases. His is a more representative series. Analysis of the present group shows that the blood pressure readings were not definitely abnormal; therefore no very high incidence of dilatation of the aorta could be expected.

GROUP IV. CARDIAC NEUROSES

This group consists of 15 patients, with an average age of 28.6 years. All patients over forty years of age were excluded. The blood pressure ranges were quite normal. The average systolic pressure was 120.5 mm. Hg, the average diastolic pressure 71.5 mm. Hg, and the average pulse pressure 49 mm. Hg. Only one case had a dilated aorta. Bayley² found dilatation in 9 per cent of 31 cases of cardiac neurosis. We have found only one other reference to the occurrence of a dilated aorta in neuroses. Norris¹⁴ describes paroxysms of dilatation of the abdominal aorta which occur chiefly in neurasthenic women with ptosis. During such attacks there is a marked localized pulsation of the abdominal aorta simulating aneurysm. Attacks are said to begin and end suddenly.

GROUP V. CONGENITAL STENOSIS OF THE AORTA

This group consists of 4 cases of coarctation of the aorta and one of subaortic stenosis. No patient was over forty years of age. The average age was 30.4 years. The average systolic pressure was 168 mm. Hg, the average diastolic 99.6 mm. Hg, and the average pulse pressure 70.8 mm. Hg. Four cases showed widening of the aortic or supracardiac shadow. Vaquez and Bordet³ believe that the dilatation of the aorta in congenital aortic stenosis is to be explained in the same way as the dilatation of the pulmonary artery in cases of congenital stenosis and that it is due to a functional distention so that it may be perceptible during life but not found after death. They also found dilatation beyond the point of stenosis. Of our 5 cases only one came to autopsy. The patient with subaortic stenosis, aged forty years, had a definitely widened and tortuous aorta by x-ray examination, and yet at post-mortem the aortic arch measured only 6 cm. in circumference and there was no evidence

of dilatation. In the other cases we have no reason to suspect aortic disease and must therefore assume that the dilatation results from increased pressure. Certainly the conditions for producing a functional dilatation are ideal in these cases. That is to say, there is throughout life an increased pressure.

TABLE I
NO PATIENTS OVER FORTY YEARS OF AGE

GROUPS	NO. OF CASES	AVERAGE AGE	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	PULSE PRESSURE	PER CENT OF CASES DILATED
Aortic insufficiency	39	19.1	129.6	44.9	84.9	25.6
Hypertension	21	25.5	202.4	130.9	72.4	42.8
Cardiac neuroses	15	28.6	120.5	71.5	49.0	6.6
Congenital stenosis of aorta	5	30.4	168.0	99.6	70.8	80.0
Hyperthyroidism	26	29.6	133.0	64.4	68.1	13.5

DISCUSSION

From a review of the literature it becomes apparent that, though isolated cases of dynamic dilatation of the thoracic aorta have been noted and a number of authors have casually mentioned its occurrence, aside from the work of Bayley and of Smith and Kilgore, no one has focused attention upon it as being relatively common. The present study indicates its rather frequent occurrence in aortic insufficiency of rheumatic heart disease, hypertension, and congenital stenosis of the aorta and a slightly less frequent occurrence in hyperthyroidism. In the hypertensive group the elevated pressures in a young individual with an elastic aorta offer the ideal condition for the development of a functional dilatation. In the group of congenital stenosis of the aorta the systolic, diastolic and pulse pressure, though all elevated, are not so high as in the hypertensives. However, the great duration of the process more than offsets the pressure differences, and dilatation is the rule rather than the exception. In the cases of aortic insufficiency and in hyperthyroidism somewhat comparable blood pressures are observed, the chief feature being a high pulse pressure. Though the present study indicates the frequent incidence of dilatation in both groups, it is more common in the aortic insufficiency cases. This is probably due to the younger ages in that group and to the higher pulse pressures. We find no evidence that dynamic dilatation is common in cardiac neuroses. We look upon dynamic dilatation as a purely mechanical process and assume that there are two factors balanced against one another, namely, the elasticity of the aorta and the intra-aortic pressures. Since we do not consider that elastic tissue has any neurogenic control, it could not be influenced by neurogenic factors.

In order to visualize what takes place in dynamic dilatation of the aorta let us assume in a given case a normal aorta in a young individual

with a normal blood pressure. Suppose the pulse pressure is at once increased from 50 mm. Hg to 80 mm. Hg. The aorta, being elastic, yields to the first systolic thrust, but during diastole it will return to its original size unless one of two things occurs. The tension of the initial thrust may exceed the elastic limit of the aorta and the vessel then will not recoil to its normal size. Thereafter it will always be somewhat dilated, and this dilatation will be demonstrable at autopsy. It is doubtful if this ever happens, for Herringham and Wills¹⁵ showed that all aortas when placed in saline for five minutes after they had been stretched with weights up to 200 gm. returned to their original size and therefore are almost perfectly elastic. The other possibility in cases of a high pulse pressure is that although the aorta may be perfectly elastic, its elastic limit having not been exceeded, its rate of recoil may be slow and a second systolic thrust strike it before it has returned to a state of rest after the first. The resulting bombardment of one systolic thrust upon another keeps the aorta dilated, though if the vessel were given a rest it would resume its former caliber which on pathological examination it is found to have. The speed of recoil depends upon the quality of the aorta. This we cannot well evaluate from a pathological study of structure. It is, in general, undoubtedly true that an abundance of elastic tissue represents a highly elastic aorta, but the presence of tissue that takes the stain for elastic tissue does not prove its functional character. It has been shown by various observers that elastic tissue varies widely in functioning power. Though we commonly look upon elastic tissue as an inert substance that responds to distortion according to pure physical principles, it is apparently true that elastic tissue is subject to fatigue. It is easy enough to visualize what happens when an elevation of pressure including the diastolic pressure occurs. Every aorta regardless of its quality, though to varying degrees, must yield when the diastolic pressure rises. The degree of dilatation will depend upon the quality of the elastic substance of the aorta. We do not know what factors alter the quality of elastic tissue. Perhaps it is influenced by heredity, or perhaps it may be altered by acute infections which, however, leave no structural evidence of damage.

In the case report given above we found an aorta which, though it was the site of disease, had not lost its elasticity. It was therefore dilated because it was continuously under a pressure of at least 135 to 150 mm. Hg diastolic and also was subjected to repeated thrusts of a pulse pressure of about 100 mm. Hg.

SUMMARY

1. A review of the literature shows very few references to dynamic dilatation of the aorta, a condition which the present study indicates

is not an uncommon occurrence. It is most common in aortic insufficiency, hypertension, hyperthyroidism, and congenital stenosis of the aorta.

2. A case is reported in which marked dilatation of the aorta demonstrable by x-ray examination was not found at pathological examination.

REFERENCES

1. Wilson, W.: Aortic Dilatation and Aneurysm, *Canad. M. J.* 12: 283, 1922.
2. Bayley, Robert H.: Dynamic Dilatation of the Thoracic Aorta, *AM. HEART J.* 8: 585, 1933.
3. Vaquez, H., and Bordet, E.: *The Heart and Aorta: Studies in Clinical Radiology*, New Haven Press, 1920 (Translation by Honej and Macy).
4. Wiggers, C. J.: *The Circulation in Health and Disease*, Philadelphia, p. 634, 1923, Lea & Febiger.
5. White, P. D.: *Heart Disease*, New York, p. 182, p. 395, 1931, Macmillan Co.
6. Scott, R. Wesley: *Diseases of the Aorta*, Oxford System of Medicine, Vol. II, part II, p. 508, Oxford Univ. Press, 1928.
7. Holmes, George: Observations in Aortic Regurgitation, *Brit. J. Radiol.* 31: 409, 1926.
8. Albutt, Sir Clifford: *Diseases of the Arteries Including Angina Pectoris*, New York, 1915, Macmillan Co.
9. Deutsch, G.: Dilatation of Vessels of Non-Syphilitic Origin, *Ztschr. f. klin. Med.* 90: 386, 1921; *Ab., J. A. M. A.* 76: 1719, 1921.
10. Hart, K.: Zur Frage der Plethora Vera, *Deutsch. med. Wehnschr.* 38: 798, 1912.
11. Sheldon, J. H.: Dilatation of the Aorta in Children Associated with Chronic Interstitial Nephritis, *Brit. J. Child. Dis.* 20: 216, 1923.
12. Evans, G.: Arteriosclerosis in Children, *Quart. J. Med.* 16: 33, 1922.
13. Smith, W. D., and Kilgore, A. R.: Dilatation of the Arch of the Aorta in Chronic Nephritis With Hypertension, *Am. J. M. Sc.* 149: 503, 1915.
14. Norris, G. W.: *Blood Pressure: Its Clinical Applications*, Philadelphia, p. 239, 1914, Lea & Febiger.
15. Herringham, W. P., and Wills, W. A.: On the Elasticity of the Aorta, Being a Contribution to the Study of Arterial Sclerosis, *Tr. Roy. Med. Chir. Soc.* 87: 489, 1904.

AN ELECTROCARDIOGRAPHIC STUDY OF VISCEROCARDIAC REFLEXES DURING MAJOR OPERATIONS*

C. C. MAHER, M.D., P. J. CRITTENDEN, PH.D., AND P. F. SHAPIRO, M.D.
CHICAGO, ILL.

THE subject of viscerocardiac reflexes during and after major operations has been investigated by others, and a review of their work is given by Owen.¹ The data herein reported are a continuance of the work of Owen,¹ and of Crittenden and Ivy.²

PROCEDURE

The electrodes used in making these electrocardiographic observations were skin suture needles about four inches long. They were placed subcutaneously in the second or third, and fifth and sixth intercostal spaces on the left side near the midline. This ruled out many of the somatic tremors which are marked with the ordinary skin contact electrode. Ressinger³ used this type of electrode in his investigation.

The control electrocardiogram was usually taken the night before the operation. When the operating schedule offered an emergency case or one of special interest, the control was taken from one-half to one hour prior to the anesthesia.

Electrocardiograms were made at various intervals during anesthesia and the operative procedures, and also from four to six hours postoperatively. Additional electrocardiograms were usually made the next day and also one week later.

The progress of the operations was observed by one of us who signalled the operator of the electrocardiograph when to take an electrocardiogram. The surgeons cooperated in synchronizing manipulations likely to give viscerocardiac reflexes with the taking of the electrocardiograms.

TYPES OF CASES

Eighty-nine cases were studied. The type of cases varied. They included: cholecystectomy, 16 patients; appendectomy, 9; gastric resection, 7; cholecystectomy and appendectomy, 4; herniotomy, 5; hemorrhoidectomy, 4; uterine fibromyomectomy, 3; hysterectomy, 4; hydrocele, 3; colostomy, 3; thyroidectomy, 3; salpingectomy, 2; exploratory laparotomy, 2; cholecystotomy, 3; perineorrhaphy, 1; enteroanastomosis, 1; nephrectomy, 1; thoracoplasty, 1; vaginal fistula, 1; salpingectomy and appendectomy, 1; cesarean section, 1; cyst of the broad ligament, 1; ovarian carcinoma, 1; ovarian cyst, 1; uterine suspension, 1; vaginal plastic, 1; tuberculous peritonitis, 1; generalized carcinomatosis, 1; lumbar sympathectomy, 1; ulnar neurolysis, 1; radial neurolysis, 1; incision of cellulitis, 1; normal deliveries, 3.

In the early part of the work a general survey was made of as many different types of operations as could be utilized. Later it seemed that viscerocardiac reflexes might be obtained best from the upper abdominal operations. Special effort was made to find cases with such complications as jaundice, pancreatitis or previous cardiac disease. Previous work demonstrated that these conditions were

*From the Departments of Physiology, Medicine and Surgery of the Northwestern University Medical School and the Department of Surgery of the Cook County Hospital, Chicago. This work has been aided by a grant from the Josiah Macy, Jr., Foundation.

likely to sensitize the viscerocardiac reflex mechanism. The cases studied included fifty-four women and thirty-five men. Their ages varied from twelve to seventy-three years.

ANESTHESIA

Various types of anesthetics were used: ether, 58 patients; ether with nitrous oxide induction, 12; nitrous oxide only, 6; nitrous oxide and local anesthesia, 2; local anesthesia, 3; spinal anesthesia, 3; peridural anesthesia, 1; avertin, 1. Two of the deliveries were conducted without anesthesia.

RESULTS

P-Wave.—The most outstanding electrocardiographic observation made during the entire series was the P-wave change which occurred with the patient under deep ether anesthesia. The P-waves would disappear with the assumption of nodal rhythm and evidence of retrograde conduction in the auricles. This occurred in twenty-eight of the fifty-eight straight ether cases, and in four of the twelve nitrous oxide ether cases. In the latter, nodal rhythm appeared only after the patient was under deep ether anesthesia. With two exceptions, it never appeared in the cases using nitrous oxide only, nor in the avertin, spinal, peridural or local anesthesia cases. These exceptions occurred in one case under spinal and in one under nitrous oxide novocain anesthesia.

Besides these nodal rhythm cases, seven patients showed a shortening of the P-R interval without actually going over into nodal rhythm. In four of these cases there was a decrease of from 0.03 to 0.04 second when the patient was brought under deep ether anesthesia. In two cases the P-R abbreviation occurred later in the operative procedure. In one case a decrease of 0.03 second was specifically noted with dilatation of the rectum, but at this point also the anesthesia was deepened by the patient's increased respirations.

Other changes noted in the P-waves were that they became depressed during deep ether anesthesia without going into nodal rhythm (two cases). They became diphasic in two cases under deep ether anesthesia. In one case they became larger in the second stage of anesthesia, only to disappear in the third. In one thyrotoxic case, the T- and P-waves were practically fused. This fusion became more marked as the tachycardia increased during the anesthesia, and was probably only a result of the increased heart rate. The P-wave was negative in one case for two hours after the operation, and then positive. In one case it was present, but decreased in size for six hours after operation, and then returned to normal size. In one case the P-R interval was increased by 0.06 second during the operation. In one case an increase of 0.04 second was noted one week after operation.

Voltage.—Certain voltage changes were found. They appeared in the excitement stage of anesthetic induction, or when the patient was

straining on the operation table, and sometimes during operative procedures. An increase in voltage was seen in one case when the pylorus was crushed and the stomach pulled down for resection. It was seen once when the gall bladder was being pulled up, once during palpation of a carcinomatous stomach. A decrease in voltage was also seen once when the appendix was being ligated, and once when the rectum was being dilated. The reaction was absent many times, however, when the surgeon, with specific force, pulled on the stomach, gall bladder, appendix, thyroid, hernial sac, uterus, hemorrhoid or adhesions, or explored the abdomen.

QRS Complexes.—QRS changes occurred in fifteen patients having ether, or ether with nitrous oxide induction, and in one patient under avertin. In one patient who was slightly jaundiced the R-wave was decreased 2 mm. during anesthesia and operative procedure but was increased 2 to 4 mm. postoperatively. In one case the S-wave deepened during the excitatory phase of the anesthesia. Dilation of the rectum caused a diphasic complex in another. In one case there was a mild but definite slurring of the QRS toward the end of the operation. In another, the QRS became widened and notched while the gall bladder bed was being packed. In one case (thoracoplasty under avertin) the QRS became widened and slurred after the patient "went bad" on the table. A week postoperatively in one hydrocele case, the wave was slurred and notched, indicating a myocardial disturbance. Postoperatively in one case the QRS complex was depressed the day after operation; in another case it increased one week later.

T-Wave.—Anesthetic induction depressed the T-waves in seven cases; in four of these they remained depressed throughout the entire operative procedure. In one case the T-waves showed some inversion during deep nitrous oxide anesthesia. They stayed flat through the ether administration and operation, but became upright again when the peritoneum was being closed. During anesthetic induction the waves increased in two other cases, disappeared in two and became more pointed in one.

The waves vanished in four cases only late in the operative procedure. They were seen to disappear with palpation of a carcinomatous mass, manipulation of the duodenum, pulling on a hernial sac, placing an appendiceal purse string, etc., but the association was neither constant nor specific. Occasionally they became inverted and sometimes diphasic. Postoperatively the wave became markedly decreased in two cases, absent in one, and negative in two.

Rates.—The changes in rates were taken as differences from the immediately preceding rate rather than from that of the control. In one thyrotoxic case, the control rate was 190 resembling an auricular flutter with 1:1 ratio. The rates were usually increased with anesthetic

induction, fluctuated irregularly with various operative maneuvers, and became normal soon after the completion of the operation.

Thirty-one cases showed an increase of from twenty to eighty beats per minute with anesthetic induction. Four showed a decrease of from fifteen to twenty-five during early anesthesia. In two cases under nitrous oxide, the rate was increased twenty and forty-five, to be decreased later by ether, sixty and forty-five respectively. One case showed a gradual increase of thirty-five during anesthesia and operative procedure. In one case there was a consistent tachycardia throughout. The following changes occurred at various intervals during operative procedure. Pulling on the gall bladder decreased the rate forty-five beats per minute in two cases and twenty-five in another. Cutting the skin was associated with an increase of forty in one case and cutting the peritoneum with an increase of fifty in another; the latter procedure caused a decrease of thirty and fifty-five in two other cases. In an appendectomy, traction on the mesentery of the appendix caused a decrease of seventy-five. In a herniotomy, traction on the sac caused an increase of thirty-five.

Extrasystoles.—Auricular extrasystoles occurred in five cases, ventricular extrasystoles in four cases and nodal extrasystoles in two. In two other cases there were both auricular and ventricular extrasystoles. The auricular extrasystoles began in one cholecystotomy case while the skin incision was being made and disappeared when the gall stone was removed. They appeared again when the peritoneum was being closed. They appeared also during incision of a hernial sac, pulling on an omentum, during clamping of hemorrhoids and packing a gall bladder bed. They were also seen, however, without operative stimuli, e.g., during the excitatory stage of anesthesia, and again one day post-operatively.

The ventricular extrasystoles appeared during palpation of a carcinomatous mass, during clamping of hemorrhoids, closing of the peritoneum, pulling on a hernial sac, and packing of a gall bladder bed. They were also seen, however, during anesthetic induction. In two cases, extrasystoles of ventricular origin were present in the controls, during anesthesia induction and postoperatively, but were absent during the operative procedure.

In a thyroidectomy under nitrous oxide, one nodal extrasystole appeared during early anesthesia. In a cholecystectomy under ether, interpolated beats of nodal origin appeared when the cystic duct was being cut.

ABNORMAL BEATS

All these electrocardiographic abnormalities were of such different character and occurred at such various intervals that a brief protocol on each patient seems desirable.

CASE 1.—Appendectomy-cholecystectomy. Ether. The patient was slightly jaundiced at the time of the operation. The R voltage was lowered about 2 mm. during anesthesia and operative procedure, increasing 2 to 4 mm. postoperatively. During the operative procedure the T-wave was depressed and a sinus arrhythmia was noted.

CASE 6.—Cholecystectomy. Ether. During the operative procedure the QRS had a phasic variation and the T-wave was flattened. The skin incision caused a new auricular complex which persisted until the removal of the gall stone. A similar change was noted when the peritoneum was sutured.

CASE 8.—Colostomy. Carcinoma of the rectum. Ether. The sino-auricular node was depressed throughout the operative procedure. The T-wave was depressed during anesthesia induction and the operative procedure.

CASE 10.—Appendectomy. Ether. The T-wave was depressed throughout the operative procedure and slowly returned to normal postoperatively. It was again depressed on the fifth day and was absent two weeks later. Cutting the peritoneum caused a depression of the sino-auricular node which was still depressed five days later.

CASE 13.—Cholecystotomy. Ether. The R voltage was markedly decreased the first day postoperatively, and the T-wave was depressed during the operative procedure. The sino-auricular node was markedly depressed during anesthesia. There was a mass in the region of the duodenum, the palpation of which caused an extrasystole of ventricular origin.

CASE 16.—Herniotomy. Ether. The T-wave disappeared with tension on the hernial sac, and there were also extrasystoles of auricular origin during the incision of the hernial sac. Nodal rhythm was present during the "painting" of the skin.

CASE 18.—Hemorrhoidectomy. Light nitrous oxide. The T-wave became negative during the operative procedure and also persisted postoperatively. Extrasystoles of auricular and ventricular origin were noted with clamping of the hemorrhoids. Dilating the rectal sphincter caused marked somatic tremors.

CASE 19.—Benign rectal tumor. Ether. The T-wave became absent during the operative procedure and negative postoperatively. The skin incision caused a complete auriculoventricular disassociation. When the fascia was reached sinus rhythm had returned.

CASE 22.—Hysterectomy. Ether. There was a slight variation in the QRS voltage with the operative procedure. Ventricular extrasystoles, three in sequence, followed by a nodal beat, occurred with the sewing of the peritoneum.

CASE 27.—Fibromyomatous uterus. Ether with nitrous oxide induction. Early anesthesia decreased the P-R interval 0.04 second, and there was also a sino-auricular block which disappeared in later anesthesia.

CASE 28.—Uterine suspension. Ether. The QRS complex was depressed after anesthesia, and the T-wave was depressed during the operative procedure and postoperatively. There was retrograde conduction and nodal rhythm with pulling on the round ligament and tube, showing simultaneous auricular and ventricular conduction. This lasted for several minutes when sinus rhythm again appeared.

CASE 29.—Strangulated hernia. Ether with nitrous oxide induction. There were extrasystoles of ventricular origin with pulling on the hernial sac and strangulated omentum. The auricular complex changed in character for three successive beats

after each extrasystole. Extrasystoles occurred at various times during the operative procedure. These changes were not noted with the control anesthetic induction or postoperatively.

CASE 31.—Appendectomy. Cholecystectomy. Ether. The QRS was notched in the control, but this was more apparent after the anesthesia was administered. There was nodal rhythm early in the operative procedure with a rate of 60. Clamping the appendix caused a return to sinus rhythm.

CASE 34.—Inoperable gastric carcinoma. Ether. The T-wave became flattened with anesthesia and remained so throughout the operative procedure. There was a change from sino-auricular to nodal rhythm.

CASE 36.—Hemorrhoids. Nitrous oxide with some ether. The P-wave became negative with clamping of the hemorrhoids and with packing. There were extrasystoles of auricular origin with dilation of the sphincter and clamping of the hemorrhoids. Ventricular escape occurred during the exploration of the rectum.

CASE 37.—Cholecystectomy and appendectomy. Ether. The T-wave was flattened postoperatively and became inverted six hours after the operation. During early anesthesia there was ventricular escape with a return to sinus rhythm which occurred twice in a short period of time.

CASE 39.—Cholecystectomy. Ether. Ventricular escape and nodal rhythm was observed when the gall bladder was under tension, and with clamping of the cystic duct.

CASE 42.—Cholecystectomy. Ether. In some instances during the operative procedure there was a retrograde conduction with nodal rhythm.

CASE 43.—Cholecystectomy. Ether. The T-wave showed some slight variation in voltage during the operative procedure. There was a complete block or ventricular escape while the peritoneum was being cut.

CASE 44.—Hydrocele. Ether. QRS complex was notched and slurred one week later showing myocardial disturbance.

CASE 45.—Gastric carcinoma. Ether. The T-wave disappeared with manipulation of the duodenum. There were extrasystoles of auricular origin with excitement during anesthetic induction, clamping of the blood vessels, and cutting of the fascia. There were also extrasystoles of ventricular origin during the first two procedures noted above.

CASE 47.—Cholecystectomy. Appendectomy. Ether. The P-wave became smaller during the operative procedure. The P-R interval lengthened 0.04-0.06 second during the operative procedure. The S voltage likewise increased. The first day, postoperatively, there was an extrasystole of auricular origin.

CASE 48.—Appendectomy. Procaine and nitrous oxide later, just after completion of incision and before locating the appendix. In early nitrous oxide anesthesia, the T-wave was absent. Ligation of the appendix caused it to become small, and while the purse string was being placed, it became negative or diphasic. It was negative with cutting the appendix and persisted postoperatively one week later. The placing of the purse string caused ventricular escape, and nodal rhythm supervened. Cutting the appendix changed the auricular complex. The P-wave became small in size and disappeared, with inversion for four beats, and then returned to normal.

CASE 49.—Fibromyomatous uterus. Ether. In early anesthesia the T-wave was inverted and diphasic with manipulation of the uterus. In exploration of the lower abdomen there was ventricular escape with supervention of nodal rhythm, and retrograde conduction was readily demonstrated.

CASE 57.—Appendectomy. Ether. A case of rheumatic heart disease. A mild waviness of the base line was suggestive of fibrillation of the auricle. The P-waves disappeared under ether.

CASE 58.—Thyroidectomy. Nitrous oxide. The control showed a very rapid rate of 190, which resembled an auricular flutter with a 1:1 ratio. There was one nodal extrasystole during early anesthesia.

CASE 59.—Cecostomy. Ether. During the early operative procedure the T-waves became more prominent. Later they were diphasic, and by the end of the operative procedure there occurred a definite but mild slurring of the QRS.

CASE 60.—Exploratory laparotomy. Nitrous oxide and ether. P-waves disappeared during deep ether. They returned later. Some flattening of the T-wave was noted during the latter part of the operation.

CASE 62.—Salpingectomy. Ether. During the course of the operation, P-waves became lower and T-waves slightly higher.

CASE 70.—Appendectomy. Nitrous oxide and ether. During deep nitrous oxide anesthesia, the T-waves showed some inversion and remained flattened through the ether anesthesia. They became upright, however, while the peritoneum was being closed, and the ether was still being given.

CASE 71.—Hysterectomy. Ether. Under deep anesthesia, the P-wave disappeared. It reappeared momentarily while the patient was changed to the Trendelenburg position. It disappeared when the ether was deepened for skin incision. It reappeared for a minute during the last stages of the operation only to disappear again until the ether was lightened.

CASE 72.—Hysterectomy. Ether. Nodal rhythm appeared for a brief interval toward the end of the operative procedure.

CASE 77.—Gastric resection. Ether. The rate slowed to 80, and the voltage increased after the pylorus was crushed and the stomach pulled out for resection.

CASE 79.—Perineorrhaphy. Ether. Nodal rhythm appeared as soon as the patient was under deep ether anesthesia.

CASE 82.—Cholecystectomy. Nitrous oxide and ether. On packing the gall bladder bed, QRS widened and became notched. The height of T-wave increased and the auricular complex disappeared. Ventricular rhythm was disturbed by probable extrasystoles.

CASE 83.—Cholecystectomy. Ether. Nodal rhythm began as soon as the patient was under deep ether anesthesia. It was associated with a mild increase in voltage.

CASE 85.—Thyroidectomy. Nitrous oxide. T-waves and P-waves were practically fused in the controls. This fusing became more marked as the rate increased during the anesthesia. Marked tachycardia (140) developed as the incision was being closed.

CASE 87.—Thoracoplasty. Avertin. The patient "went bad" on the table. At this point the QRS widened and slurred, and a marked tachycardia developed.

CASE 89.—Cholecystectomy. Ether. The P-wave was enlarged under moderate ether anesthesia but disappeared under deep ether anesthesia. It reappeared during

the early operative procedures, but disappeared when the ether was deepened in the later stages of the operation. At this point also, namely when the cystic duct was being cut, interpolated beats of nodal origin appeared.

CASE 90.—Cholecystectomy. Ether. Under deep ether anesthesia the P-waves became diphasic. In several of the electrocardiograms there were numerous small diphasic complexes which were probably artefacts but might have represented auricular activity.

CASE 91.—Cholecystectomy. Ether. Patient jaundiced. The only change noted was the appearance of nodal rhythm.

CASE 92.—Cholecystectomy. Ether. Nodal rhythm under deep ether anesthesia.

CASE 93.—Cholecystotomy for acute pancreatitis. Ether. Nodal rhythm under deep ether anesthesia.

CASE 94.—Cholecystectomy. Ether. Patient jaundiced. Low voltage while the patient was straining. Nodal rhythm began when the patient was fully under. P-waves returned for a short time during the course of probing the common bile duct but disappeared again while the same procedure was still under way. P-waves reappeared only when the ether was stopped.

Disappearance of Control Abnormal Beats.—There was also another group of patients in whom abnormal beats were present in the control electrocardiogram, but were conspicuously absent later.

CASE 20.—Cesarian section. Ether. The control showed a sinus arrhythmia which disappeared with the operative procedure.

CASE 24.—Neurolysis of the ulnar nerve. Ether. The control waves showed extrasystoles of ventricular origin which were present with administration of the anesthetic but disappeared during the operative procedure and reappeared post-operatively.

CASE 32.—Tuberculous peritonitis. Ether with nitrous oxide induction. The control showed extrasystoles of ventricular origin which disappeared during the operative procedure and reappeared postoperatively.

Somatic Tremors.—Three other cases showed marked somatic tremors with certain operative procedures.

CASE 4.—Vaginal fistula. Ether. There were marked somatic tremors with dilation of the rectum.

CASE 9.—Hydrocele. Ether. There were tremors with puncturing of the hydrocele.

CASE 18.—Hemorrhoidectomy. Light nitrous oxide. There were marked somatic tremors with dilation of the rectum.

Obstetrical Cases.—Three obstetrical cases were followed during delivery from the first to the third stages. No marked changes were noted except in the following cases. During pain in the first stage there was an increase of 70 in the heart rate. In the latter part of the first stage, the rate slowed. Very marked somatic tremors were noted in all three cases.

DISCUSSION

The most frequent important cardiac change found in these observations was disappearance of the P-wave with assumption of nodal rhythm. Deep anesthesia was probably the single most important factor in eliciting it. The P-wave change was seen practically only in these cases in which deep anesthesia was used. Thus it was seen in thirty-two of the seventy cases in which ether was used, and only twice in the nineteen cases in which some lighter anesthetic was given. Among the ether cases it was seen especially in those cases requiring deeper anesthesia. Thus it appeared in fourteen of the twenty gall bladder cases, and in four of the five herniotomies, and in none of the three hydroceles. P-wave changes never appeared before the patient was under moderate or deep anesthesia. They usually appeared some time during the third stage of anesthetic induction and before any operative manipulation had begun. They usually disappeared near the close of the operation when the anesthetic was discontinued.

Occasionally nodal rhythm did not appear until late in the operative procedure. In these cases the patients were not deeply anesthetized until some particular manipulation late in the operative procedure required it. Such manipulations varied greatly in type, including pulling on the round ligaments, dilation of the rectum, ligating the cystic duct, etc. The anesthesia was always deepened at these points, but it is impossible to state in these instances whether the deepening of anesthesia or the operative manipulation was responsible for the nodal rhythm.

In four cases nodal rhythm appeared, then disappeared and reappeared several times during the operation. It was observed that its appearance and disappearance corresponded to those periods in which the anesthesia was increased and decreased, respectively. It was also noted that during the course of a single procedure, e.g., probing the common bile duct, the P-wave would at first appear normal. Then the P-R interval would gradually shorten and the P-wave become depressed or notched until it was lost in the ventricular complexes. It might then appear superimposed on some limb of the QRS or on the R-T segment. It would seem here that the operative manipulation had induced the nodal rhythm, but within a minute or less while the same procedure was under way, the process might reverse, and normal sinus rhythm be reestablished.

Deep anesthesia, however, is not the only factor in the production of these changes. Thirty-eight of the seventy ether cases failed to show the P-wave changes. Even with the same operation and same depth of anesthesia, they sometimes appeared and sometimes did not. There were probably several uncontrollable factors which influenced susceptibility to these changes. These clinical observations, however,

did not establish what those factors were. Age and sex were not important. The patients varied from twelve to seventy-three years in age. Cardiac changes were as frequent in the older patients as in the younger. They were as common in women as in men. Moreover, the condition of the patient had little to do with these changes. We selected certain toxic and septic patients, one very anemic patient, one emaciated patient and one in profound shock. The cardiac changes produced at operation were no different in character and frequency from those seen in patients in good condition. Apparently the general condition of the patient is not related to his susceptibility to cardiac changes. Thyrotoxicosis also failed to play any rôle except in giving a basal tachycardia. We had two cases in which there was previous cardiac disease, one rheumatic heart disease, the other coronary sclerosis, and these two also failed to show any noteworthy cardiac changes.

In a previous paper,² evidence obtained from dogs suggested that icterus sensitized the vagal mechanism, and thus might account for the greater incidence of cardiac irregularities obtained in icteric animals on distention of the biliary passages. Three of our gall bladder patients were jaundiced. The changes produced in them, however, were no different in character and frequency from those produced in the nonjaundiced gall bladder patients. Though none of these factors could be established singly as of direct importance, it may be that some summation of them is what finally determines an individual's susceptibility to cardiac changes.

The type of anesthesia was not important except as it controlled the depth of anesthesia. In a recent article by Hill⁴ it is stated that chloroform was more toxic to the heart than other anesthetics. The most outstanding irregularity he found was the production of multiple extrasystoles of ventricular origin. They occurred primarily during anesthetic induction, disappeared with deep anesthesia, and were not related to the operative procedure. Such changes were not observed in this series. However, chloroform was not used in any of our cases. Ether was used in almost all cases in which cardiac changes were produced. The three exceptions, one case under spinocain, one under avertin, and one under nitrous oxide and novocain, demonstrate, however, that it is not the ether which is specifically responsible for these changes, but rather the depth of anesthesia.

Minor changes in the P-wave and shortening of the P-R interval are interpreted in the same light as the development of nodal rhythm. The voltage changes were probably a general somatic reaction rather than a specific viscerocardiac reflex. Their association with any operative manipulation was neither constant nor specific, and they appeared also during anesthesia before any operative procedure was started, and even after operation and anesthesia had been stopped.

The same may be said of the T-wave changes. QRS changes indicate myocardial disturbance. They too appeared to be related to the toxicity of deep anesthesia rather than to any particular operative stimulus. Only twice in fifteen times in which it was observed did it seem that the QRS change was closely associated with an operative manipulation. In one case it was the packing of a gall bladder bed; in the other it was the evacuation of an empyema which apparently produced the change.*

Extrasystoles and slowing of rate appeared as sharper responses. They were seen several times directly associated with some operative visceral stimulation, and it seemed that here on occasion a true viscerocardiac reflex had been produced. Extrasystoles appeared in thirteen of the eighty-nine cases. In two cases they appeared during anesthetic induction, and in one case postoperatively. Slowing of the pulse appeared in eleven of the eighty-nine cases. It appeared in six cases during anesthetic induction. In ten cases extrasystoles appeared in immediate association with a definite operative maneuver, such as pulling on a gall bladder (two cases), palpating a carcinomatous mass, crushing a hemorrhoid, incising a hernial sac (two cases), pulling on the omentum, etc. In four cases the pulse slowed while the gall bladder was being pulled, in two cases while the peritoneum was being cut, and once during traction on the mesentery.

The type of operation did not seem to be important. An especially large number of gall bladder patients (twenty cases) were studied because previous work² indicated that viscerocardiac reflexes might best be obtained from the biliary tract. Only four of the twenty showed extrasystoles. The type of operative manipulation did not seem to be important because extrasystoles appeared after all types of unrelated stimuli. Only two of the gall bladder cases showed extrasystoles in definite association with manipulation of the biliary tract. Four bradycardial responses were directly related to pulling on the gall bladder, yet they were also seen after other manipulations. From the proximity of the stomach to the celiac plexus and diaphragm it seemed that gastric operations might be likely to elicit viscerocardiac reflexes. Rössinger³ found marked changes with a case of carcinoma of the cardia. We, too, found electrocardiographic changes in four cases of operation for gastric neoplasm, but three other cases were negative. In the four positive cases, only once was a bradycardia related to direct manipulation of the stomach. Extrasystoles were not seen in any of the gastric cases. In these observations there was no constant, specific connection between type of operation or type of operative stimulus and electrocardiographic disturbance. Only the

*Bettman and Priest showed that if thoracoplasty caused a simple lateral shift of the heart, no electrocardiogram changes were produced. If, however, it caused rotation of the heart on its A-P axis (so that flow through the great vessels at the base was compromised), changes were produced.

bradycardia on pulling the gall bladder was suggestive of such a connection. Even in positive cases when the surgeon was asked several minutes later at the same operation, or at some other similar operation, to repeat the particular manipulation with special force intended to elicit the cardiac disturbance, almost always nothing happened. The failure to repeat the result at the same operation might be explained as a fatigue inhibition. The failure to repeat it at a subsequent operation might be explained on the basis of some uncontrollable variable.

The difficulty of obtaining electrocardiographic changes in response to visceral stimulation and particularly the difficulty of establishing any constant or specific connection between them does not, however, refute the importance of neurological connection between the viscera and the cardiac rhythm reflexes. The fact remains that in a certain, albeit small, percentage of cases electrocardiographic changes were produced which were directly related, in time at least, with a definite operative stimulus. The association of such changes with visceral stimuli has been demonstrated previously by experimental studies on animals² and by observations on normal unanesthetized human subjects. The routine conditions of clinical surgical procedures introduced several factors, however, which could not arbitrarily be eliminated, and which inhibited the cardiac responses. The positive results which were obtained were probably due to the fact that in exceptional instances there was sufficient gap in the inhibitions to admit a viscerocardiac response.

The deep anesthesia itself, though apparently responsible for the P-wave changes and perhaps partly responsible for the T-wave and QRS changes, may have been the most important factor in preventing the appearance of extrasystoles, bradycardias and other gross changes. The preoperative morphine and atropine which all our patients routinely received may have had similar inhibitory effects. Thus it has been found that in experimental animals the injection of apomorphine, by causing nausea and vomiting, will elicit cardiac irregularities in a certain proportion of cases. Deep anesthesia, however, or large doses of morphine will abolish this effect (Crittenden). The pathway for the cardiac response is largely vagal; and atropine alone, it has been found, will also abolish the viscerocardiac reflexes produced by experimental apomorphine visceral excitation. In three of our own cases there was an abnormal cardiac rhythm during the controls, during anesthetic induction and postoperatively. During the operative procedure, however, with the patients under deep anesthesia, and morphine and atropine the cardiac abnormalities vanished. These three cases demonstrated quite definitely that deep anesthesia and morphine and atropine could abolish cardiac irregularities. It is conceivable that they exerted a similar inhibitory effect on the rest of our cases,

and thus could have succeeded in preventing the production of these irregularities. *From a clinical standpoint, it may well be considered a favorable circumstance that the routine conditions of major surgical procedures automatically suppress the development of cardiac changes under visceral stimulation.*

CONCLUSIONS

During major surgical procedures the most frequent electrocardiographic change is suppression of the P-wave and assumption of nodal rhythm. This occurred in thirty-four of the eighty-nine cases, and was probably chiefly a function of deep anesthesia.

The type of anesthetic, the age and general condition of the patient, the cardiac condition of the patient, the type of operation or of operative procedure or the underlying pathology for which it was done did not seem to be important in producing this change.

Extrasystoles appeared in ten cases and bradycardia appeared in seven cases in apparent direct association with a visceral stimulation. No constant or specific relation could be established, however, between the surgical procedure and the cardiac response.

REFERENCES

1. Owen, S. E.: A Study of Viscerocardiac Reflexes, *AM. HEART J.* 8: 496, 1933.
2. Crittenden, P. J., and Ivy, A. C.: A Study of Viscerocardiac Reflexes, *AM. HEART J.* 8: 507, 1933.
3. Ressinger, H.: Electrocardiographic Investigation During Surgical Procedure, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 40: 504, 1927.
4. Hill, I. G. W.: The Human Heart in Anesthesia, *Edinburgh, M. J. N. S.* 39: 533, 1932.
5. Lenox, W. G.: Graves, R. C., and Levine, S. A.: An Electrocardiographic Study of Fifty Patients During Operation, *Arch. Int. Med.* 30: 57, 1922.
6. Marvin, H. M., and Pastor, R. B.: The Electrocardiogram and Blood Pressure During Surgical Operation and Convalescence, *Arch. Int. Med.* 35: 768, 1925.
7. Buchbinder, W. C.: The Electrocardiogram in Experimental Obstructive Jaundice, *Proc. Soc. Exper. Biol. & Med.* 27: 371, 1930.
8. Buchbinder, W. C.: Experimental Obstructive Jaundice, *Arch. Int. Med.* 42: 743, 1928.
9. Bettman, R., and Priest, W.: Electrocardiographic Studies Before and After Chest Operations, *AM. HEART J.* 5: 366, 1930.

Department of Clinical Reports

OBSERVED ONSET OF BUNDLE-BRANCH BLOCK WITH CORONARY THROMBOSIS 45 HOURS LATER*

C. BRUCE PERRY, M.D.
BRISTOL, ENGLAND

THE following case appears worthy of record because of the fact that the development of a bundle-branch block was observed electrocardiographically without any symptoms or change in physical signs.

A. P., aged fifty-nine years, railway-shunter. November 17, 1933, referred to hospital by Dr. A. N. P. Milner, his panel doctor, for further investigation.

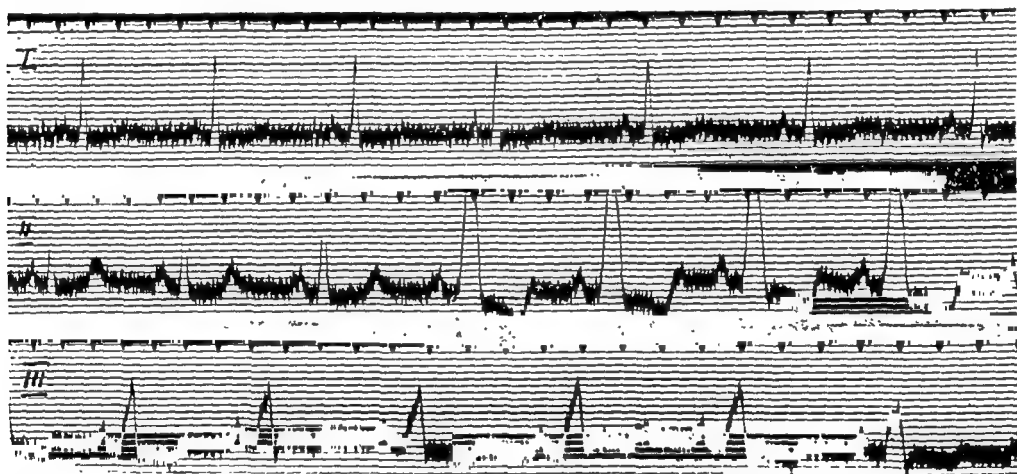


Fig.1.—Electrocardiogram showing the onset of bundle-branch block in Lead II. Time marker indicates fifths of seconds.

Patient complained of attacks of "heaving" pain in the middle of the chest. This pain was caused by walking, particularly up a hill, and passed off in one or two minutes when he stopped. He had noticed some dyspnea on exertion during the past year, but the first severe attack of pain was six weeks ago. The pain was usually associated with dyspnea.

No previous illnesses of importance.

Family History.—Father died of a "seizure" aged sixty years. Mother died aged sixty-five years from "old age." One brother died of "cancer" aged sixty years. Other siblings alive and well.

Examination.—Radial and brachial arteries definitely thickened. No venous congestion in the neck. Apex beat and cardiac dullness normal, heart sounds faint except the second sound at the aortic area which was accentuated. Blood pressure

*From University Center of Cardiac Research, General Hospital, Bristol, England.

190/100 mm. Retinal arteries appeared arteriosclerotic and the veins were full. There were no abnormal physical signs in the lungs, abdomen or nervous system. The urine contained no albumin or sugar. Wassermann reaction was negative. An x-ray film showed no appreciable cardiac enlargement. An electrocardiogram (Fig. 1) showed a normal tracing in Lead I and in the first half of Lead II, after which the ventricular complexes suddenly assumed the features of a bundle-branch block. Another electrocardiogram taken one and one-half hours later (Fig. 2) showed a bundle-branch block of "indeterminate" type in all three leads. There were no symptoms associated with this change in the character of the electrocardiogram and no alteration in the clinical physical signs. The patient stated that he felt quite well and was unwilling to remain in hospital.

Subsequent history.—He returned home and was apparently well until November 19, when he was seized with a severe substernal pain at 9 A.M. following an attack of flatus. The skin was cold and clammy and he complained of faintness. The pain lasted until 2 P.M. On this day the patient was visited by Dr. A. N. P. Milner, to whom I am indebted for this history. November 22, no further pain but complaints of great weakness. Suddenly his speech became very difficult and slurred,

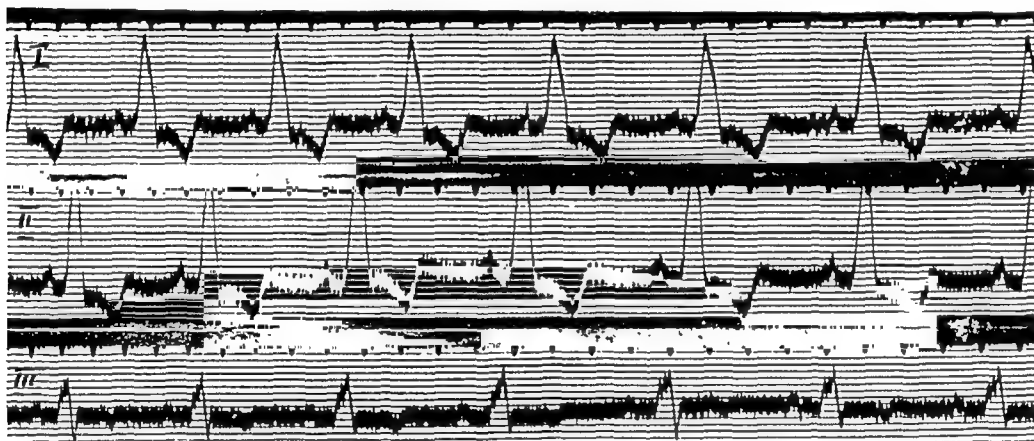


Fig. 2.—Electrocardiogram taken one and one-half hours later. Time marker indicates fifths of seconds.

the mouth was drawn to the right side, and he lost the use of his left arm and leg. After this short periods of consciousness and unconsciousness alternated with complete hemiplegia. Death on November 26, one week after the attack of pain. No post-mortem examination.

COMMENT

It is difficult to correlate the onset of the bundle-branch block with a coronary thrombosis, since the characteristic pain did not occur until forty-five hours later. In view of the subsequent history of what appears quite definitely to be a cardiac infarction with later cerebral embolism from a detached intraventricular thrombus, it is difficult to avoid the conclusion that the electrocardiographic changes were the result of an organic myocardial lesion. Further, in those cases of bundle-branch block in apparently normal healthy adults, which are associated with attacks of paroxysmal tachycardia, reported by Wolff, Parkinson and White,¹ and by Wolferth and Wood,² there occurred a

shortening of the P-R interval with the onset of the abnormal ventricular complex. In this case, however, the P-Q interval (which is more strictly comparable) is unchanged by the onset of the bundle-branch block. It is tempting to speculate that the occlusion of the main coronary branch was of slow development and that a deposit of fibrin and platelets occluded a small branch supplying the lower part of the A-V bundle while the first electrocardiogram was being taken, and that the further growth of this thrombus was so slow that the lumen of the main artery was not occluded until forty-five hours later.

REFERENCES

1. Wolff, L., Parkinson, J., and White, P. D.: AM. HEART J. 5: 685, 1930.
2. Wolferth, C. C., and Wood, F. C., AM. HEART J. 8: 297, 1933.



Fig. 3.

Fig. 2.

Fig. 1.

it was slowly absorbed. The patient gradually improved and was discharged in eight weeks, symptom free, with a normal sized heart (Fig. 3) and after absorption of the remainder of the pericardial fluid.

Numerous laboratory examinations were made. In summary these were: negative blood Wassermann with all antigens, normal blood cholesterol, sugar, and urea

nitrogen, and normal phenolsulphonephthalein excretion. Repeated urine examinations for tubercle bacilli were negative. Fragility of the red blood cells was somewhat increased, hemolysis beginning at 0.525 and being complete at 0.425; reticulocyte count was 3.4 per cent. Bleeding and clotting times and clot retraction were within normal limits. The van den Bergh test showed a negative direct reaction, and an indirect reading of 0.2 units. Icterus index was 10. Roentgen examinations of the skull, spine, pelvis, femora, and ribs were negative for any evidence of malignant disease. Intravenous urogram, done because of the persistence of red blood cells in the urine, was negative; however, a retrograde pyelogram of the left urinary tract showed a slight irregularity in the lower calices suggesting a possible pyelonephritis. An electrocardiogram contained some auricular extrasystoles, slurring of the QRS complexes and slight evidence of myocardial damage.

During hospitalization, the temperature was practically normal at all times; the pulse, however, remained between 100 and 110. On discharge, red blood count was 4,500,000, hemoglobin 88 per cent, and white blood cells 9,000, with a normal differential picture. Urine was negative except for a few red blood cells.

A "follow-up" in September, 1933, showed the patient to be in good general health with a normal tolerance for exercise. The heart was not enlarged (by percussion, roentgenogram, or orthodiagram), the sounds were of good quality, and no murmurs or thrills were found. The second aortic sound was moderately accentuated. An electrocardiogram again revealed some evidence of myocardial damage. Blood pressure was 210 mm. systolic, and 100 diastolic, as compared with his previously normal readings. Abdominal examination revealed the liver extending from 4 to 5 fingerbreadths below the right costal margin and firm, smooth, and not tender. The spleen was barely palpable. No other abnormal abdominal masses could be felt. Because of his freedom from symptoms, the patient could not be induced to return to the hospital for further studies.

DISCUSSION

Based on the reported cases, the causes of hemopericardium include the following: (1) tuberculosis¹⁻¹¹; (2) rupture of sclerotic coronary vessels¹²⁻¹⁴; (3) wounds of the heart or aorta, and rupture of an aneurysm¹⁵⁻²³; (4) neoplasms²⁴⁻³⁰; (5) hemorrhagic diseases³¹⁻³⁴; (6) a post-infectious sequel^{35, 36}; (7) chronic nephritis.^{37, 38}

Tuberculous pericarditis is not infrequently accompanied by a hemorrhagic effusion. This has seldom consisted of whole blood; moreover the prognosis is usually fatal, with a life expectancy of from one to twelve months from the date of discovery of the effusion. In a recent review by Kornblum et al.⁶ of 17 cases of tuberculous pericarditis, only one patient is said to have had bloody fluid.

Rupture of sclerotic coronary vessels with production of hemopericardium has usually been recognized only post-mortem. Alcott¹³ in a review of the literature found only 31 cases of rupture of one or both coronary arteries. It is unlikely that this would occur without some associated change in the electrocardiographic findings. No disturbances of note were found in the electrocardiograms of our patient.

Traumatic wounds of the heart, pericardium or aorta are not uncommon. It seems unlikely, however, that the slight fall against the

wall which our patient experienced was responsible for a traumatic wound of these parts. During the past decade, ruptured aneurysms have become a rarity.

Tumors of the heart and pericardium are rare and are usually without symptoms. Only one record has been found of a primary tumor of the heart diagnosed during life.²⁵ Primary tumors of the pericardium are usually sarcoma or lipoma, although rare instances of carcinoma and endothelioma have been reported. Hemorrhagic effusion is not uncommon from pericardial or cardiac neoplasms. Tumors of any of the organs may give rise to metastasis to the heart. However, the duration of life is usually short and reaccumulation of fluid is rapid.

Practically every hemorrhagic disease has been reported in association with hemopericardium. Leucemia, purpura hemorrhagica, hemophilia, and primary anemia can easily be ruled out by appropriate blood studies. History of adequate diet and lack of other symptoms makes scurvy improbable in our patient. In view of the slight reticulocytosis, and increased fragility of the red blood cells to hypotonic salt solution, the enlarged liver and palpable spleen, hemolytic ictero-anemia is a definite possibility. However, urobilin could be demonstrated at no time in the urine, and the van den Bergh test showed no essential change. If this be the correct diagnosis, the occurrence of a hemopericardium with no other signs of hemorrhage is extremely unusual.

Pericardial effusion secondary to chronic nephritis is usually straw colored or very slightly hemorrhagic. In only 1 of 18 autopsied cases of pericarditis in chronic nephritis did Barach³⁸ find a frankly bloody fluid.

Another possibility which has been suggested is the simultaneous occurrence of multiple angiomas, liver, pericardium, and other organs being affected. This possibility could not be tested in our patient without exploration, which was refused by the patient.

The cause of the bloody effusion in our patient remains unknown; however, in spite of an almost normal electrocardiogram, we are inclined to believe that the hemopericardium resulted from rupture of a sclerotic coronary vessel in a hypertensive individual.

The diagnostic features of hemopericardium, apart from the character of the fluid, are in no outstanding way different from those of a serous effusion. Tapping when necessary to relieve cardiac tamponade is best performed just outside the apex or in the costoxiphoid angle.

Although the prognosis is poor, with a fatal termination in the large majority of cases, yet numerous reports of cure following evacuation of a hemopericardium can be found.^{8, 36, 39, 42}

SUMMARY

1. A case with massive pericardial effusion of blood is reported with a clinical cure following two paracenteses with removal in all of 1,500 c.c. of almost undiluted blood.

2. The etiology of hemopericardium is briefly reviewed.

REFERENCES

1. Hirtz, E.: Pericardite hemorrhagique de nature tuberculeuse, *Rev. gén. de clin. et de thérap.* 12: 689, 1898.
2. Souques, M. A.: Pericardite hemorrhagique d'origine tuberculeuse, *Bull. Soc. Anat. de Paris* 64: 611, 1889.
3. Hedblom, C.: Primary Tuberculous Pericarditis, *S. Clinics N. America* 1: 1411, 1921.
4. Riesman, D.: Primary Tuberculosis of the Pericardium, *Am. J. M. Sc.* 122: 6, 1901.
5. Dillon, E. S.: Tuberculous Pericarditis With Tuberculosis of the Myo- and Endocardium, *M. Clin. N. America* 10: 253, 1926.
6. Kornblum, K., Bellett, S., and Ostrum, H. W.: Roentgenologic Significance of Tuberculous Pericarditis, *Am. J. Roentgenol.* 29: 203, 1933.
7. Hudelo: Pericardite hemorrhagique chez un tuberculeux (epanchement de deux litres; ponction du pericarde), *Bull. Soc. Anat. de Paris* 63: 1024, 1888.
8. Hughes, T. A., and Yusuf, M.: Pericarditis With Effusion With Infarction of the Heart in Young Phthisical Subject, *Brit. M. J.* 1: 794, 1931.
9. Monnier and Durbin: Pericardite tuberculeuse hemorrhagique, *Gaz. med. de Nantes* 25: 15, 1907.
10. Amadrut: Cure of Tuberculous Pericarditis With Bloody Effusion, *Bull. et mém. Soc. d. hôp. de Paris* 47: 816, 1923.
11. Waller, W. E.: Tuberculosis of the Pericardium, *Lancet* 2: 278, 1923.
12. Edwards, A. T.: Hemorrhage in the Pericardium, *M. J. Australia* 2: 761, 1928.
13. Alcott, C. T.: Rupture of Coronary Artery; Hemopericardium, Report of Case and Review of Literature, *New England M. J.* 204: 760, 1931.
14. Jones-Evans, E. J. L.: Hemopericardium Resulting From Rupture of the Right Coronary Artery Secondary to Chronic Interstitial Nephritis, *Practitioner* 109: 184, 1922.
15. Williamson, A. J.: An Unusual Case of Hemopericardium, *Lancet* 2: 1743, 1909.
16. Bird, U. S.: Hemorrhage Into the Pericardium, *M. Rec. N. Y.* 52: 701, 1897.
17. Evans, W. A.: Some Cases of Hemopericardium, *Birmingham M. Rev.* 26: 20, 1889.
18. Dyson, J. M. and Schnabel, T. G.: Pericardial Hemorrhage—Aneurysm of Aorta With Rupture, *Pennsylvania M. J.* 35: 27, 1931.
19. Naismith, W. J.: On the Symptom of Pain in Slow Pericardial Hemorrhage, *Lancet* 2: 949, 1889.
20. Warrington: Hemorrhage Into the Pericardium, *Liverpool M. Chir. J.* 24: 128, 1904.
21. de Massary, E., and Boquien, Y.: Infaret of the Myocardium With Hemopericardium, *Bull. et mém. Soc. med. d. hôp. de Paris* 53: 1430, 1929.
22. Fahr, T.: Fatal Hemorrhage in Heart Following Therapeutic Injections of Drugs and Puncture of Pericardium for Drainage, *Deutsche med. Wehnschr.* 54: 1550, 1928.
23. Pallasse, E., and Lambert, M.: Aortic Aneurysm of Dissecting Form With Hemopericardium, *Lyon méd.* 141: 519, 1928.
24. Hill, H.: Primary Round Cell Sarcoma of the Pericardium, *Arch. Path.* 5: 626, 1928.
25. Yater, W. M.: Tumors of the Heart and Pericardium, *Arch. Int. Med.* 48: 627, 1931.
26. Collins, M.: Large Lipoma of Epicardium, *Gior. di clin. med.* 12: 1324, 1931.
27. Campagna, M., and Hauser, G. H.: Cancer of Epicardium, *J. A. M. A.* 90: 1362, 1928.
28. Keller, W. L., and Callender, G. R.: Neurofibroma Arising on Pericardial Pleura, *Tr. Am. Surg. Assn.* 474, 1930.

29. Businco, A.: Fibroepithelial Tumors of the Inner Layer of the Pericardium, *Tumori* 10: 99, 1923. *Ab. J. A. M. A.* 81: 1244, 1923.
30. Everingham, S.: Primary Endothelioma of the Pericardium, *S. Clin. N. America* 11: 975, 1931.
31. Abeille: De la pericardite hemorrhagique liee au scorbut; ses points de separation de la pericardite ordinaire, et surtout de la pericardite hemorrhagique par violence hyperemique; trois observations, *Gaz. d. hôp. Par.* 26: 283, 1853.
32. Vance, B. M., and Graham, J. E.: Periarteritis nodosa complicated by intrapericardial hemorrhage, *Arch. Path.* 12: 521, 1931.
33. Eshner, A. A.: Hemorrhagic Pericarditis, *Tr. Path. Soc. Philadelphia*, 1887-89, 14: 155, 1891.
34. Nordmann, M.: Two Cases of Profuse Diapedesis With Effusion Into the Pericardium and Fatal Outcome, *Deutsches Arch. f. klin. Med.* 147: 100, 1925.
35. Dowd, C. N.: Pericardotomy for Hemorrhagic Pericarditis, *Ann. Surg.* 57: 768, 1913.
36. Sears, G. G.: A Case of Hemorrhagic Pericarditis Due to Pneumococcus; Aspiration; Recovery, *Boston M. & S. J.* 139: 293, 1898.
37. Ledoux, S.: Pericardite hemorrhagique du cours d'un mal de Bright, *J. d. se. med. de Lille* 1: 80, 1900.
38. Barach, A. L.: Pericarditis in Chronic Nephritis, *Am. J. M. Sc.* 163: 44, 1922.
39. Stewart, W.: Notes of a Case of Hemorrhagic Pericarditis Associated With Presence of *B. Coli Communis*; Paracentesis; Recovery, *Edinburgh J. M. n.s.* 15: 158, 1904.
40. Mores, J. L.: A Case of Traumatic Hemopericardium, *Boston M. & S. J.* 150: 240, 1904.
41. Bryant, F.: Report of a Case of Hemorrhagic Pericarditis; Aspiration; Recovery, *Boston M. & S. J.* 152: 521, 1905.
42. Shattuck, F. C.: Pericarditis With Large Hemorrhagic Effusion in a Patient With Grave's disease; Repeated Puncture; Double Dry Pleurisy; Recovery, *Boston M. & S. J.* 125: 491, 1891.

SYPHILITIC AORTITIS WITH ANEURYSM OF THE INNOMINATE ARTERY AND OCCLUSION OF THE LEFT COMMON CAROTID ARTERY*

LAURENCE E. COOLEY, M.D., AND FRANK P. McNAMARA, M.D.
DUBUQUE, IOWA

OCCCLUSION of the mouths of the coronary arteries due to syphilis is not an uncommon pathological finding. Syphilitic occlusion of larger arteries would seem to be a much rarer condition.

Recently Motley and Moore¹ reported a case of syphilitic aortitis in which the opening of the left common carotid and subclavian arteries "would not much more than accommodate the shaft of a small pin." They mentioned similar reports of syphilitic occlusion made by Preisdorfer² in 1878 and Darling and Clark³ in 1915. Several other reports of syphilitic occlusion were found in the older literature. In 1882 Whitney and Blake⁴ described a case of aneurysm of the innominate artery with the orifice of the left common carotid artery only 2 mm. in diameter and the orifice of the left subclavian artery entirely obliterated. In 1885 Suckling and Dendy⁵ reported a case of innominate aneurysm in which the orifice of the left common carotid artery was obliterated, while Blackman⁶ reported an innominate and aortic aneurysm in which the opening of the left subclavian artery was a "mere chink." In 1902 while discussing surgery of aneurysms Fenger⁷ wrote, "In some cases of aneurysm of the aorta as well as the innominate artery the left common carotid artery is either obliterated or very weak." Kaufmann⁸ states that occasionally the larger vessels of the arch of the aorta are narrowed or occluded in syphilis of the aorta.

CASE REPORT

A white laborer, aged sixty-two years, came under observation in May, 1932, complaining of a dull aching pain in the left shoulder and arm, and a loss of forty pounds of weight. The onset was insidious and the symptoms had been noticed for one year. Relatives reported that the patient's mental reactions had become much slower during the past five years and that he had complained of being dizzy at times during the past three years.

There was no history of previous illness. The family history was not known. There were two children living and well. The wife was in good health. She had had no miscarriages or stillbirths. There was no history of venereal disease.

Physical examination: The patient was a well-developed male, rather thin, and not acutely ill. The pupils were unequal and irregular and did not react to light. Under the right sternoclavicular joint a pulsating tumor could be felt. No arterial

*From the Departments of Medicine and Pathology, Finley Hospital, Dubuque, Iowa.

pulsation could be palpated on either side of the neck. The sternal ends of both clavicles were enlarged and tender. In the first interspace to the right of the sternum a soft blowing to-and-fro systolic and diastolic murmur could be heard. There was no increase in the supracardiac dullness. Examination of the heart, abdomen, and nervous system revealed no abnormal findings. On the prepuce of the penis was a small whitish scar. There was some limitation of motion of the right elbow and shoulder. There was no arterial pulsation to be obtained anywhere along the right arm or at the wrist. The nails of the right hand were slightly cyanotic. Blood pressure, right arm 0, left arm 96/50. Fluoroscopy of the chest showed a diffuse pulsating enlargement of the arch of the aorta. There were



Fig. 1.—Photograph of heart and great vessels: (a) dilated ascending aorta; (b) aneurysm of innominate artery; (c) thrombosed right common carotid artery; (d) subclavian artery and thyroid axis; (e) occluded left common carotid artery; (f) enlarged left subclavian artery.

no pathological findings in the x-ray pictures of the right shoulder and elbow and in the urine and blood Wassermann examinations.

The patient was given mild antisyphilitic treatment for the next six weeks with some improvement at first. On May 27, 1932, the blood pressure was 70/56 in the right arm and 126/54 in the left arm. At the end of six weeks the patient was too weak to come into the office for treatment. He was next seen September 15, 1932. The pulsating tumor was visible above the right sternoclavicular joint. The patient was not seen again until April 12, 1933. The pulsating tumor could be seen to extend 3 cm. above the clavicle and was 3 cm. in diameter. During the two months preceding, when the patient turned on his left side he had a sensation of smothering and began to lose consciousness. This was promptly relieved when the patient was turned on his back again. He died April 14, 1933.

The points of special interest at autopsy were: a moderate diffuse dilatation of the ascending and transverse aorta with fine linear striations characteristic of luetic mesoaortitis; a diffuse dilatation of the innominate artery, the length being 6 cm. and the diameter 2.5 cm.; an old organized thrombus, found in the upper part of the innominate aneurysm, and a fresher thrombus found in the lower part; organized and canalized thrombi in the right common carotid artery and the right subclavian artery and all its branches except the inferior thyroid; absence of the orifice of the left common carotid artery, represented by a depression in the wall of the aorta; above the occlusion an organized thrombus which extended to the bifurcation into the internal and external carotid arteries; an unusually large left subclavian artery; and an osteochondritis of the sternal ends of both clavicles. Microscopically the aorta and innominate artery showed areas of perivascular round cell infiltration and an increase in the scar and connective tissue with fragmentation of elastic tissue; the orifice of the left common carotid artery was occluded by connective tissue infiltrated with nests of round cells about the blood vessels; hyalinization and round cell infiltration were seen around many of the vessels in the region of the pons; in the testes there was a diffuse increase of connective tissue between the tubules. These were interpreted as the results of syphilis.

COMMENT

This case presented many interesting pathological changes. The blood supply was one of the most remarkable features. Almost no blood reached the head through the right common carotid and right vertebral arteries and none through the left common carotid artery. At autopsy the heart, aorta and as much of the neck as possible were removed *in toto*. Unfortunately we did not suspect the occlusive lesion until the arteries were dissected out several days later. There was no evidence of thrombosis in the left internal and external carotid arteries. It is probable that blood from the left subclavian reached these arteries through the deep cervical artery by an anastomosis with the descending branch of the occipital artery, which is a branch of the external carotid artery. The symptoms of dizziness, retarded mental reactions and the sensation of smothering when lying on the left side can easily be explained on the basis of this unusual blood supply. It seems remarkable that the patient could live at all with such a large part of the ordinary blood supply obstructed.

There have been many reports of aneurysm of the innominate artery associated with syphilis of the aorta. Reviewing the older literature one may say that syphilitic occlusion of the larger branches of the aortic arch also is not an extremely rare pathological finding. Darling and Clark³ concluded from their study that occlusions of the carotid, innominate, subclavian, renal or mesenteric arteries occurred in 3.7 per cent of syphilitic cadavers. Perhaps a more diligent search at autopsy would lead to similar reports now.

Clinical diagnosis of these occlusive lesions may be made if one has this possibility in mind when examining cases of syphilis of the cardiovascular system. Certainly it is easy to determine whether or not

there is a pulsation in the carotid and subclavian arteries. Vague and unusual symptoms may thus be explained. Finally a correlation of autopsy findings and clinical symptoms may lead to the formation of a definite symptom-complex in syphilitic occlusions of the larger branches of the aorta.

REFERENCES

1. Motley, Lyle, and Moore, Robert: Obliterating Syphilitic Arteritis, J. A. M. A. 100: 656, 1933.
2. Preisdorfer, P.: Virchow's Arch. f. path. Anat., 1878, p. 73 (quoted by Motley and Moore¹).
3. Darling, S. T., and Clark, H. C.: Arteritis Syphilitica Obliterans, J. M. Res. 32: 1, 1915.
4. Blake, John G., reported by Mr. H. B. Whitney: Aneurysm of the Innominate, Boston M. & S. J. 106: 418, 1882.
5. Suckling, R., and Dendy, W.: A Case of Innominate Aneurysm, Lancet 2: 245, 1885.
6. Blackman, J. G.: Diffused Innominate Aneurysm, Lancet 1: 928, 1887.
7. Fenger, Christian: Aneurysm of the Innominate Artery, Med. Standard 25: 12, 1902.
8. Kaufmann, E.: Lehrbuch der Speziellen Pathologischen Anatomie, Berlin und Leipzig, 1922, p. 93, Vereinigung Wissenschaftlicher Verleger.

Department of Reviews and Abstracts

Selected Abstracts

Hart, Andrew D., Wood, J. Edwin, and Daughton, A. D.: Rheumatic Fever in Piedmont, Virginia. I. Incidence and Clinical Manifestations. *Am. J. M. Sc.* 187: 352, 1934.

Two hundred instances of rheumatic disease observed during a six-year period at the University of Virginia Hospital have been studied in an effort to determine the approximate incidence of the disease as a whole and to note particularly the relative occurrence of its various manifestations.

It would appear that rheumatic fever is of frequent occurrence in central Piedmont, Virginia, where it is three times as common as in the tidewater section of the same state. The arthritic forms of the disease, although mild and of such short duration as to suggest that they may at times escape detection, are relatively frequent and tend to recur in a fairly high percentage of cases. Serious and permanent damage to the heart is evidenced in a surprisingly large number of persons with rheumatic fever.

Elliot, Albert H.: Anemia as the Cause of Angina Pectoris in the Presence of Healthy Coronary Arteries and Aorta: Report of a Case. *Am. J. M. Sc.* 187: 185, 1934.

A fifty-five-year-old woman with chronic anemia and repeated epistaxes had attacks of angina pectoris over a period of three years which became extremely severe with the occurrence of a febrile illness. At necropsy an hypertrophied but otherwise normal heart was found. The coronary arteries were thin walled and dilated; detailed study revealed no lesions in their walls other than occasional flecks of lipoid on the intima; the aorta was unchanged. The physiological evidence is reviewed which indicates that anemia, by increasing cardiac output, may cause myocardial hypertrophy; that under these circumstances the adaptive limit of the coronary flow may be reached in the resting state and easily exceeded under additional physiological circulatory burden and that the resultant myocardial ischemia might express itself as an anginal seizure. It is suggested that such a mechanism could well explain both the clinical and the pathological findings in this case. This study demonstrates that angina pectoris may occur in the absence of disease of the coronary arteries, myocardium or aorta.

Laplace, Louis B., and Crane, Martin P.: Observations on the Production of Pain and Fatigue in Muscular Ischemia and Their Relationship in Angina Pectoris. *Am. J. M. Sc.* 187: 264, 1934.

Observations were made in a series of 36 subjects on the relationship of ischemia to the development of pain and fatigue in the contracting muscles of the arm. The development of both pain and fatigue was favored by arrest of the circulation, but the two phenomena were not affected to the same extent by dif-

ferent degrees of ischemia or by variations in the type of work. In many cases the relatively early development of fatigue was able to terminate exercise before the manifestation of severe pain. Constitutional nervous sensitivity did not appear to affect the pain of muscular ischemia.

On the basis of these observations, it is concluded that constitutional nervous sensitivity is unlikely to be a significant factor in the occurrence of angina pectoris. The rarity of cardiac pain in congestive heart failure and its absence in many cases of coronary obstruction may be explained by the fact that the development of cardiac fatigue maintains the maximal work of the heart at a level below the threshold of pain production.

Levy, Robert L., Bruenn, Howard G., and Kurtz, Dorothy: Facts on Disease of the Coronary Arteries, Based on a Survey of the Clinical and Pathologic Records of 762 Cases. Am. J. M. Sc. 187: 376, 1934.

A statistical analysis was made of the autopsy and clinical records of 762 cases of coronary artery disease observed at the Presbyterian Hospital during the period from 1910 to 1931. The facts apparent as a result of this survey are to be regarded as applying to this material; no general conclusions are drawn.

Arteriosclerosis was the most common lesion, having been found in 97.2 per cent of the cases. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the coronary blood flow in 5.7 per cent. Syphilis did not play a rôle in predisposing to coronary sclerosis. It was present no more frequently in patients with coronary disease than in those without it.

In 2,877 consecutive autopsies, lesions of the coronary arteries were found in 25.9 per cent. This is a strikingly high figure.

In half of the cases showing sclerosis in the coronaries, the lesions were "slight" or "moderate"; in many of these instances, no functional impairment of the cardiac circulation was induced by such lesions. The lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developing with advancing years.

In this series of autopsies, the incidence of coronary disease showed a slight but steady increase throughout a twenty-two-year period; but the increase was not nearly so great in the proved cases as was indicated by the figures based on clinical diagnosis alone. The reasons in explanation of these facts have been given.

Coronary artery disease increased at all ages, but the increase was particularly noteworthy between the ages of twenty-five and forty-four years. There was a predominance of males. The number of cases increased in both sexes.

Occupation did not appear to play a significant part in determining those whose vessels were affected. The largest percentage of coronary cases was found among foremen and skilled workers.

The clinical diagnosis of coronary disease is being made with greater accuracy as well as with increased frequency. Many cases are latent and probably cannot be recognized during life. Even in the presence of calcification or stenosis, the diagnosis was made clinically in but 16 per cent of the cases during the years from 1920 to 1931. During this same period, coronary thrombosis was correctly diagnosed in only 43 per cent of the cases.

Arteriosclerotic heart disease was the most frequent primary cause of death. Cardiac insufficiency was the commonest terminal event.

The increase in the incidence of affections of the coronary arteries is not to be regarded as a matter of concern. Rather should it be a source of satisfaction

The functional classification of pregnant cardiac patients has been considered, and it was noted that 5 cases out of Classes 1 and 2 (a) decompensated, which is at variance with the work of Pardee who claims that Classes 1 and 2 (a) have an excellent prognosis. Other factors, in the author's opinion, must be considered in addition to the functional classification, such as the age of the patient, the family environment, the duration of the heart disease, and the extent of valvular damage.

Most of the cases that decompensated did so before the onset of labor, and there was no relationship demonstrated between the month of pregnancy and the onset of decompensation.

The mortality was 7.5 per cent, which falls within the mortality range of from 5 to 10 per cent as reported by reliable observers. Two of these deaths were probably preventable. Consideration of the mortality of the patients having prenatal care and those who did not, shows a death rate of 2.2 per cent in the former and in the latter 20 per cent, thus demonstrating the importance of prenatal care.

The limited follow-up showed that 56 per cent were not worse following pregnancy, while 43 per cent were. The need for further follow-up study to determine what happens to the cardiac mother and her child after the lying-in period is obvious.

Master, Arthur M.: Right Ventricular Preponderance of the Heart. The significance of Ventricular Preponderance and T-Wave Inversion in the Human Electrocardiogram. Am. J. M. Sc. 186: 714, 1933.

Electrocardiograms from 173 cases in the last four years showing right ventricular preponderance of the QRS group were studied. The groups of diseases found to be associated with right ventricular preponderance are: (1) chronic valvular disease (57 per cent) with mitral stenosis alone or associated with other valvular lesions; (2) degenerative heart disease (21 per cent); (3) noncardiac diseases such as thyroid disease, bronchial asthma and emphysema and finally congenital heart disease and syphilis. Female individuals predominated in patients with chronic valvular disease and male individuals in the degenerative heart disease group.

Right ventricular preponderance with inversion of T_2 and T_3 is associated with the most marked right ventricular enlargement, with the largest hearts, with the most marked enlargement of the pulmonary conus and the left auricle, with markedly increased lung markings and congestion in the lungs and with the highest mortality (33 per cent). Right ventricular preponderance with inversion of T_2 alone is associated with a less marked degree of these anatomical changes and a mortality of 15 per cent and finally in right ventricular preponderance with any inversion of the T-wave at all, the least changes occur and the mortality is only 7 per cent.

Auricular fibrillation was present in 40 per cent of the patients showing right ventricular preponderance with both T_2 and T_3 inverted, 17 per cent when T_3 alone was inverted, and only 7 per cent with no T-wave inversion.

Kissin, Milton, Ackerman, Walter, and Katz, Louis N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle-Branch Block in Man. Am. J. M. Sc. 186: 721, 1933.

The present investigation was made to discover whether changes in the heart's position caused a noticeable shift of the electrical axis in six individuals with so-called right bundle-branch block. Electrocardiograms were taken in various positions of the body and in different phases of respiration. Some degree of

The functional classification of pregnant cardiac patients has been considered, and it was noted that 5 cases out of Classes 1 and 2 (a) decompensated, which is at variance with the work of Pardee who claims that Classes 1 and 2 (a) have an excellent prognosis. Other factors, in the author's opinion, must be considered in addition to the functional classification, such as the age of the patient, the family environment, the duration of the heart disease, and the extent of valvular damage.

Most of the cases that decompensated did so before the onset of labor, and there was no relationship demonstrated between the month of pregnancy and the onset of decompensation.

The mortality was 7.5 per cent, which falls within the mortality range of from 5 to 10 per cent as reported by reliable observers. Two of these deaths were probably preventable. Consideration of the mortality of the patients having prenatal care and those who did not, shows a death rate of 2.2 per cent in the former and in the latter 20 per cent, thus demonstrating the importance of prenatal care.

The limited follow-up showed that 56 per cent were not worse following pregnancy, while 43 per cent were. The need for further follow-up study to determine what happens to the cardiac mother and her child after the lying-in period is obvious.

Master, Arthur M.: Right Ventricular Preponderance of the Heart. The significance of Ventricular Preponderance and T-Wave Inversion in the Human Electrocardiogram. Am. J. M. Sc. 186: 714, 1933.

Electrocardiograms from 173 cases in the last four years showing right ventricular preponderance of the QRS group were studied. The groups of diseases found to be associated with right ventricular preponderance are: (1) chronic valvular disease (57 per cent) with mitral stenosis alone or associated with other valvular lesions; (2) degenerative heart disease (21 per cent); (3) noncardiac diseases such as thyroid disease, bronchial asthma and emphysema and finally congenital heart disease and syphilis. Female individuals predominated in patients with chronic valvular disease and male individuals in the degenerative heart disease group.

Right ventricular preponderance with inversion of T_2 and T_3 is associated with the most marked right ventricular enlargement, with the largest hearts, with the most marked enlargement of the pulmonary conus and the left auricle, with markedly increased lung markings and congestion in the lungs and with the highest mortality (33 per cent). Right ventricular preponderance with inversion of T_3 alone is associated with a less marked degree of these anatomical changes and a mortality of 15 per cent and finally in right ventricular preponderance with any inversion of the T-wave at all, the least changes occur and the mortality is only 7 per cent.

Auricular fibrillation was present in 40 per cent of the patients showing right ventricular preponderance with both T_2 and T_3 inverted, 17 per cent when T_3 alone was inverted, and only 7 per cent with no T-wave inversion.

Kissin, Milton, Ackerman, Walter, and Katz, Louis N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle-Branch Block in Man. Am. J. M. Sc. 186: 721, 1933.

The present investigation was made to discover whether changes in the heart's position caused a noticeable shift of the electrical axis in six individuals with so-called right bundle-branch block. Electrocardiograms were taken in various positions of the body and in different phases of respiration. Some degree of

shift in electrical axis appeared with change in position of the heart in every case. Twice, marked changes in the electrical axis appeared, and the electrocardiogram of a so-called right bundle-branch block changed to the indeterminate type of bundle-branch block. The position of the heart as well as the site of the blocked bundle-branch determine the direction of the QRS of the electrocardiogram of bundle-branch block. This may be the explanation of certain apparent contradictions in the findings of previous students of bundle-branch block.

It is suggested that electrocardiograms heretofore interpreted as left and right bundle-branch block be reported simply as intraventricular block or "bundle-branch block configuration" and that no attempt be made to locate the blocked bundle-branch from the electrocardiographic appearance alone.

France, Richard: The Large Q-Wave in Lead III of the Electrocardiogram. *Am. J. M. Sc.* 187: 16, 1934.

An analysis is made of 103 electrocardiograms characterized by a normal sinus rhythm with a significant Q-wave in Lead III. A study of the histories of the cases with reference to the electrocardiographic findings is presented. The pathological alterations in the hearts of 12 of the cases are given. The relation of the Q-wave mechanism to occlusion of the right coronary artery and infarction of the posterior basal portion of the interventricular septum is discussed.

The results of the present study are in accord with the observations of others to the effect that the large Q-wave in Lead III while sometimes present in the absence of heart disease, is frequently associated with serious myocardial damage. Furthermore, it is indicated that when this wave and additional evidence of myocardial disease exist in the record, angina pectoris is often present. Postmortem findings support the view that the deep Q_3 is commonly seen as part of the evidence of the electrocardiographic change occurring after thrombosis of the right coronary artery with subsequent infarction of the posterior base of the left ventricle and adjacent portion of the interventricular septum.

Bunta, Emil: Blood Pressure Variations in Tuberculosis. *Am. Rev. Tuberc.* 29: 335, 1934.

The object of the present study was to determine the range of arterial tension in tuberculosis. A greater divergence from the range of absolute normal pressures was noted in tuberculous than in normal patients with the same sex, age, and weight. It was found that pulse pressures manifest the widest variations chiefly at the expense of systolic pressures. Variations from normal arterial tension are directed mostly toward hypotension levels. The trend in tuberculosis is toward relative hypotension rather than absolute hypotension levels. Conspicuous hypotension pressures are predicated on either pathological extent or clinical activity of tuberculous lesions. Of the two factors, clinical activity is the principal determinant. Progressive lowering pressures especially pulse pressures, parallel tuberculous activity, the degree of which is enhanced as the disease approaches the far advanced stage.

The practical import of these considerations is their application in the diagnosis, prognosis, and treatment of tuberculous patients. From a diagnostic point of view, blood pressure observations are chiefly useful as clues or as confirmatory facts in the evaluation of clinical data. The trend of recurrent individual measurements toward normal findings speaks well for ultimate arrest of the disease. A progressive lowering of blood pressure, especially pulse pressure, calls for a guarded prognosis. The management of tuberculous patients, based on a program

of rest or exercise, discontinuance or resumption of employment, preference of dispensary supervision or sanatorium care, depends in no small measure on information derived from the individual blood pressure record.

Berconsky, Isaac: *The Blood-Respiratory Function in Black Cardiacs of Ayerza.* *Semana med.* 1: 1569, 1933.

This study is based on ten patients with so-called Ayerza's disease (cardiacos negros of Ayerza). These patients had an old chronic bronchopulmonary process with emphysema and developed an intense cyanosis without evident cardiac insufficiency as a cause of the cyanosis. Unless interrupted by an intercurrent process, six patients after several years showed a congestive cardiac failure which in several of the cases became the cause of their death.

Argentine authors, pupils of Professor Ayerza, as well as authors of other countries, attribute the intense cyanosis and other symptoms and signs which these patients present, chiefly to a sclerosis of a branch of the pulmonary artery, to the cardiac failure, or to the reduction of the alveolar field in the lungs. According to the determinations carried out by the writer, it was found that due to the rigidity of the thorax, the vital capacity of these subjects is diminished strongly between 40 and 68 per cent of normal. Since the tidal flow of air is also low, there is an alveolar hypoventilation with diminution of the oxygen alveolar tension (average 64, 33 mm. Hg) with a rise in the tension of carbon dioxide (average 63, 27 mm. Hg). The low alveolar oxygen tension is the reason for the low arterial saturation (average 77, 92 per cent). The rise of the alveolar CO₂ tension determines the carbon dioxide excess (high alkaline reserve with P_H normal) and serves as a compensating measure. The great quantity of the arterial reduced hemoglobin found also in the capillary vessels (average 7.46 grams) explains logically the cyanosis (cyanosis arterial). Factors which help to intensify the cyanosis are the increased quantity of hemoglobin existing, the rise of CO₂, and the development of a dilated capillary bed which these patients present. When the cardiac insufficiency appears, the cyanosis tends to be intensified, due to the circulatory congestion (cyanosis mixta). The inhalation of oxygen will modify the arterial cyanosis.

The writer concludes that the cyanosis which is a symptom whereby the condition is called cardiacos negros is due to alveolar hypoventilation.

Eppinger, Eugene C., and Midelfart, Peter A. H.: *Stenosis of the Isthmus (Coarctation) of the Aorta.* *Am. J. M. Sc.* 185: 528, 1933.

Three typical cases of coarctation of the aorta are presented and discussed briefly with emphasis on the history and physical findings. The salient point to be drawn from these cases is the fact that evidence of hypertension or hypertensive disease in a young adult without renal disease should suggest the possibility of coarctation of the aorta before considering the case as one of idiopathic hypertension. A less important though none the less striking feature is intermittent claudication of the legs in the same period of life.

Book Review

DIE TONUSKRANKHEITEN DES HERZENS UND DER GEFÄSSE: IHRE BIOLOGIE UND THERAPIE. By Dr. J. Pal. Julius Springer, Vienna, 1934. 228 pages and 20 illustrations.

In this monograph Professor Pal succeeds in combining a discussion of the biological basis of variations in muscle tone—particularly in muscle tone as it affects the heart and blood vessels—and a practical handbook written with clinical insight. In the first part of the book Dr. Pal discusses the cellular basis of tonicity, a function which he ascribes to the sarcoplasm as opposed to the kinetic function of the fibrillae of the muscle cells. He then considers the variations in tone of the heart and vessels, in health and in disease, as regulated by the nervous system and as affected by toxins and by drugs. In the second part of the book he turns to the clinical picture resulting from hyper- and hypotonicity. Particularly interesting is his discussion of primary permanent hypertonicity of the arteries, which he considers as an independent, usually hereditary, disease of the blood vessels, leading to hypertension (“essential hypertension”), hypertrophy of the heart, arterial and arteriolar sclerosis, and other anatomical changes. He stresses the importance of the psychic factor on p. 134, saying: “The majority of patients with hypertonicity have—as long as they know nothing of their illness—no, or only slight, subjective symptoms. As soon as they learn that their condition is not normal, they feel sick, complain of their troubles and seek to find complaints. They are sick nervously and should be treated accordingly.” Dr. Pal takes up the symptoms, complications, treatment and prognosis, emphasizing the fact that many members of hypertensive families live to old age. The entire book gives evidence of the author’s wide reading, independent work, and wise clinical viewpoint.

E. II.

The American Heart Journal

VOL. 9

AUGUST, 1934

No. 6

Original Communications

ACUTE PULMONARY CONGESTION AND CARDIAC ASTHMA IN PATIENTS WITH MITRAL STENOSIS*

SYLVESTER MCGINN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

ACUTE pulmonary congestion with or without cardiac asthma is most commonly observed with failure of the left ventricle.¹ There is, however, a much smaller group of patients with mitral stenosis who suffer similar attacks, and in such cases the left ventricle is not primarily involved. The clinical records of patients with mitral stenosis and acute pulmonary congestion have been reviewed by us to determine what characteristics differentiate this condition from that more frequently seen due to left ventricular failure.

Cardiac asthma is a term applied to a kind of dyspnea peculiar to organic heart disease. It is paroxysmal in nature, with distressing wheezing respiratory difficulty similar to that seen in bronchial asthma; it may or may not be accompanied by the expectoration of blood-tinged frothy sputum. Sudden failure of the left ventricle which has been weakened by the strain thrust upon it by hypertension, a lesion of the aortic valve, or coronary thrombosis causing myocardial infarction is primarily responsible for the greater number of cases. As the inefficient ventricle fails to expel all of its contents into the general circulation, blood piles up in the pulmonary field and through the mechanism of a reflex nervous action initiates a paroxysm of rapid breathing accompanied by wheezing (asthmatic) respiration. The attacks usually occur at night when the individual is reclining in a horizontal position and are due then most likely to the stasis of blood in the pulmonary vessels as the result of the position and of the diminished output of the weak left ventricle during sleep. Cardiac asthma may or may not be associated with moist râles in the lung bases, depending upon whether or not the failure is of sufficient degree to cause only vascular engorge-

*From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital.

ment or whether it exceeds this point to produce actual edema and hemorrhages into the alveoli. In one of Merklen's² lectures published by Heitz in 1908 it is stated that cardiac asthma is due usually to failure of the left ventricle, that in such a condition the lungs are generally clear of evident edema, but that there is a type associated with acute pulmonary edema in which there are moist râles at the lung bases, cough, and expectoration of serous sputum. Riesman³ in 1907 described acute pulmonary edema occurring at night with or without asthmatic breathing, in cases of arteriosclerotic heart disease.

ACUTE PULMONARY CONGESTION WITH MITRAL STENOSIS

The literature contains very little concerning the group of cases in which there is acute pulmonary congestion, with or without asthmatic breathing, as the result of mitral stenosis.

Vaquez⁴ has stated that although pulmonary congestion in mitral stenosis is usually a slow and insidious process, there are acute forms associated with overexertion; he erroneously referred to this pulmonary congestion as failure of the right heart. In discussing pulmonary edema in mitral stenosis, Robinson⁵ said, "Paroxysmal attacks resembling asthma are sometimes seen. Cough and expectoration, sometimes bloody or blood-streaked, occur. Hemoptysis is not uncommon." Gallavardin⁶ in 1921 presented a number of cases to illustrate three types of acute pulmonary edema: (1) that in which the left ventricle fails as a result of rheumatic myocarditis, (2) that due to chronic mitral and aortic endocarditis, and (3) that in which it is secondary to pure mitral stenosis. In the second group he presented two cases having mitral stenosis and an associated aortic lesion. One was a woman of thirty-three years who had had slight attacks when she overexerted herself and four severe attacks with expectoration of frothy sputum without any known provocative cause. The other was a woman fifty-six years of age who complained of violent attacks of smothering at night, one of which required venesection. In the third group he included four cases. The first was a woman thirty-five years old who had nocturnal smothering immediately on getting into bed, and an hemoptysis once a week sufficient to fill a basin. A woman forty-three years old had severe dyspneic attacks after coitus or unusual effort. Another woman thirty-five years of age had violent smothering attacks with the expectoration of bloody sputum following coitus and twice after a warm tub bath. The fourth case was a woman fifty-two years old who had severe attacks of dyspnea with expectoration of frothy sputum and a whistling in her chest when she walked fast. All these patients had dyspnea on effort; two had no peripheral evidence of cardiovascular failure; and digitalis failed to relieve the symptoms in three.

In 1923 Saloz and Frommel⁷ reported the case of a woman thirty-seven years old with pure mitral stenosis. She had fallen while hurry-

ing in the street and was brought into the hospital cyanotic, in a cold sweat, breathing rapidly, and with frothy sputum coming from the mouth. A venesection proved to be very beneficial for the immediate attack, but she died some days later. The post-mortem examination showed a mitral stenosis with a large left auricle and right ventricular hypertrophy.

A case with discussion has recently been presented by Thums,⁸ the patient being a twenty-eight-year-old man with mitral stenosis who suffered attacks of rapid breathing, hemoptysis, and precordial pressure following the exertion of skiing and snowshoeing. He improved while on digitalis therapy and abstinence from exercise.

THE PRESENT SERIES

We have reviewed a series of 20 cases of our own showing mitral stenosis associated with acute pulmonary congestion. Of this group, 10 had mitral valve disease alone, whereas the other 10 had a coexisting aortic lesion or hypertension. All of the second group had cardiac asthma, while 5 of the former had definite wheezing, the other 5 having severe paroxysmal attacks of dyspnea with hemoptysis or pink frothy sputum but without a clear history of wheezing. The average ages of the two groups when last heard from was 31.3 and 50 years respectively, half of the patients of the second group being over 50 years of age whereas none of the first group had reached their fiftieth year. These figures should be contrasted with those in a series of 272 cases of cardiac asthma of all etiologies that we have recently reported,¹ 90 per cent of whom, or 246 patients, were over 50 years of age; 96 per cent, or 260 cases, of that series showed no mitral stenosis and so may be compared with interest with the present series of 20 cases with mitral stenosis (Table I).

Eight of our 10 patients having mitral stenosis complicated by hypertension or aortic valve disease have died, after an average duration of life from the first attack of asthma of 1.9 years. The other two patients are in fair health to date, having survived eight years and five years respectively, an average of 6.5 years, which exceeds the expectancy of two years derived from the analysis of the above-mentioned group of 272 cases. Six of the 10 patients in the group of patients with uncomplicated mitral stenosis are living, but their activity must through necessity be greatly limited. Their average duration of life since the first attack of pulmonary edema has been 3.5 years. The average duration of life of the four patients who have died was 3.9 years from their first attacks of pulmonary edema to death. Two of these four patients died during attacks of pulmonary edema, and the other two died after progressive myocardial failure. It is of interest to note that the paroxysmal attacks ceased to recur in 4 of the patients with complicated mitral stenosis,

while each of two of the uncomplicated cases had one attack with hemoptysis and thereafter no more attacks.

Exertion in some form or other was the factor precipitating the attacks of acute pulmonary congestion in 7 of the 10 cases with mitral stenosis plus strain on the left ventricle and in 8 of the cases with pure mitral stenosis. A survey of our general series of cardiac asthma without mitral stenosis indicated that only 23, or 8 per cent, had attacks

TABLE 1
ACUTE PULMONARY CONGESTION. A COMPARISON OF CASES WITH AND WITHOUT MITRAL STENOSIS

	MITRAL STENOSIS WITHOUT CAUSE FOR LEFT VENTRICULAR HYPERTROPHY	MITRAL STENOSIS WITH A LESION TO CAUSE LEFT VENTRICULAR HYPERTROPHY	CASES OF A FORMER SERIES WITHOUT MITRAL STENOSIS
Number	10	10	260
Sex Males	6	7	196
Females	4	3	64
Cardiac asthma	5	10	260
Number who have died	4	8	232
Number over 50 years of age	0	5	239
Average age at onset of attacks	26	47	58
Duration since onset of attacks to last report of living patients	3.5	6.5	4.1
Average age at death or last report	31.3	50	59.6
Duration in years from onset of at- tacks to death	3.9	1.9	1.6
Rheumatic history	7	6	11
Attacks brought on by exertion	8	7	23
Attacks brought on by coitus	3	2	
Attacks brought on by paroxysmal tachycardia	5	1	
Frank hemoptysis	7	1	50
Frothy sputum	7	6	70
Mitral insufficiency	3	8	5
Aortic stenosis and insufficiency	0	4	8
Aortic insufficiency	0	3	48
Hypertension	0	5	167
Angina pectoris	0	4	44
Auricular fibrillation	3	3	29

initiated by exertion, the vast majority occurring while the patient was in bed and at rest during the night; of those 23 patients 3 had rheumatic mitral disease, 5 had luetic aortitis, 4 had arteriosclerotic coronary disease, and 11 had hypertension. In 12 of those patients the attacks were so frequent as to occur either in the day or in the night. The types of exertion most frequently found to produce attacks in our present series of 20 cases were coitus in 5, bathing in 3, and frequently excitement and fast walking. Five of the uncomplicated cases of mitral stenosis had pulmonary congestion with the onset of attacks of paroxysmal tachycardia. We believe that this difference in the factors precipitat-

ing attacks of acute pulmonary congestion in patients with and without mitral stenosis is of special significance.

The clinical histories show that one of our 10 cases with complicated mitral stenosis had frank hemoptysis in contrast to 7 of the 10 uncomplicated cases, while the presence of frothy sputum was noted 6 and 7 times respectively in the two groups. Angina pectoris coexisted with cardiac asthma in 4, and auricular fibrillation in 3, of the cases of our group with mitral stenosis and left ventricular hypertrophy, whereas none of the 10 patients with uncomplicated mitral stenosis had angina pectoris and 3 had auricular fibrillation. A history of having had either rheumatic fever or chorea was noted in the case of 7 of the patients with uncomplicated mitral stenosis and of 6 of the patients with complicated mitral stenosis. In the latter group aortic stenosis and insufficiency occurred together in 4 cases and aortic insufficiency without stenosis of clinical importance in 3; hypertension was present in three. Mitral insufficiency was noted clinically in 8 of the complicated cases and in 3 of the uncomplicated series.

Clinical or roentgenographic studies presented evidence indicating left ventricular hypertrophy in all the cases having hypertension or aortic disease associated with the mitral stenosis. X-ray evidence was available in 8 of the other 10 cases, and all showed "mitral shaped" hearts with enlarged left auricles and prominence in the region of the pulmonary conus. General enlargement of the heart was seen in 4 of these cases, but it was thought to be of right-sided origin, and in no case was left ventricular enlargement noted. Neither of the remaining 2 cases of uncomplicated mitral stenosis showed enlargement of the heart to the left by percussion in the fifth intercostal space. Nine patients in the group with mitral stenosis complicated by another lesion had electrocardiograms taken, three of which showed auricular fibrillation and two showed an abnormal axis deviation, to the left in both instances. Electrocardiograms were also made on 9 of the patients with uncomplicated mitral stenosis, two of which showed auricular fibrillation, one auricular flutter, four large P-waves, and 5 a right axis deviation.

Postmortem Examinations of Cases With Uncomplicated Mitral Stenosis.—Three hearts of the 10 cases of our series with uncomplicated mitral stenosis were examined post-mortem.

The first of the post-mortem examinations was made on a man thirty-two years old, who died six hours after the onset of acute pulmonary congestion. The heart weighed 560 grams. The right ventricular wall thickness varied between 5 and 8 mm. in thickness, while the left ventricular wall was 10 mm. in thickness. The left ventricle was full-sized, the left auricle considerably dilated, and the chambers on the right side were markedly dilated. The mitral valve was noted as being button hole in type with fibrocalcereous changes; the opening measured $1\frac{1}{2}$ cm. by 5 mm. The aortic valve was normal. Edema of the lungs was present, the pulmonary tissue being described as of spongy consistency and salmon colored in appearance. The liver was small.

The second case was that of a thirty-five-year-old woman who died with acute pulmonary edema. The heart weight was 325 grams; the right ventricular wall measured 10 mm. in thickness, and the left ventricular wall measured only 11 mm. The mitral valve was markedly stenosed, measuring only 3.3 cm. in circumference; it was not calcified. The aortic valve was negative. Pulmonary congestion was present in the lungs, which had large crepitant areas.

The third case was that of a twenty-eight-year-old man who died after six weeks of progressive failure. The heart weight was 528 grams, and the right and left ventricular walls measured 6 mm. and 10 mm. respectively. There was slight dilatation of the left ventricle and considerable enlargement of the left auricle and of the chambers on the right side of the heart. The mitral valve consisted of a fibro-calcareous mass surrounding a crevice-like slit. The aortic valve was normal. The lungs were voluminous, of a leathery consistency, and yielded a moderate amount of frothy fluid. One pulmonary infarct was noted. The liver was of firm consistency and had a nutmeg appearance.

DISCUSSION

Gallavardin⁶ believed that acute pulmonary edema took place as a consequence of the failure of the left auricle in cases of uncomplicated mitral stenosis. He observed that these attacks occurred only when there was a normal rhythm of the auricles and when they were not tremendously enlarged. In our cases which correspond to his, one had auricular flutter, 3 had auricular fibrillation, and 5 had attacks of acute pulmonary congestion with paroxysmal auricular tachycardia or fibrillation. X-ray films showed left auricular enlargement in all of our 8 patients with uncomplicated mitral stenosis who had roentgenograms made.

The theory of Saloz and Frommel⁷ with regard to acute pulmonary edema consequent to mitral stenosis is that there is a failure of the left ventricle. Their conception of the mechanism was based upon the experimental work of Henderson and Prince,⁹ who demonstrated the closely controlled relationship between the right and left ventricles. The work consisted of measuring the systolic outputs under various pressures in the cat's heart, and the inference drawn was that the greater the pressure in the pulmonary circuit the greater would be the systolic output of the left ventricle; hence great pulmonary congestion would be inhibited. It was also shown that when the pressure in the pulmonary vessels was low, the output of blood per beat of the left ventricle would be diminished and thus desanguination of the lungs would be avoided.

One factor is present, however, in the problem under discussion to which Saloz and Frommel⁷ failed to give full consideration, and that is the effect of mitral stenosis on the normal flow of blood. Henderson and Prince⁹ observed that the pressures described in their work on the hearts of normal cats were not invariable and depended to a great degree on the tonus of the heart and the integrity of the valves. The hypertrophy and dilatation of the left auricle and of the right chambers in mitral stenosis are strong evidence that this lesion (mitral stenosis) disturbs the equilibrium existing between the greater and lesser cir-

culations and tends to prevent the left ventricle which may be of normal size and tonus from fulfilling its usual performance of work and sending out a normal amount of blood.

There are certain features that distinguish acute pulmonary congestion when mitral stenosis is present from that in which there are hypertrophy, dilatation, and failure of the left ventricle. The burden of the strain imposed by the stenosis of the mitral valve is borne by the left auricle, the pulmonary vessels, and the right heart. As might be expected, the incidence of a rheumatic infection is high in those cases with mitral stenosis, occurring in 13 of our 20 cases, which figure compares with that of only 11 patients thought to have had rheumatic heart disease in our previously reported series of 260 cases of cardiac asthma without mitral stenosis.

Acute pulmonary edema with uncomplicated mitral stenosis appears at an earlier age, and the prognosis is better for duration of life than in the cases with left ventricular enlargement and failure. Frank hemoptysis also is more common in cases of uncomplicated mitral stenosis. Exertion or paroxysmal tachycardia is the precipitating factor of the pulmonary congestion in nearly every case of uncomplicated mitral stenosis; without tachycardia the patient is free from attacks. It is a striking fact that digitalis fails to be as beneficial in this group in which there is mechanical difficulty as it is in those cases with left ventricular strain and failure.

Oppenheimer and Schwartz¹⁰ have recently reported 3 cases having paroxysmal pulmonary hemorrhages, the patients being young individuals with mitral stenosis and without any known cause for left-sided hypertrophy. A post-mortem examination was made on one of the cases. Palpitation was a common symptom preceding the dyspneic spells, two of which were accompanied by asthmatic breathing, and pulse rates of 170, 160, and 140 were noted during attacks in the three patients. Electrocardiograms on one patient were reported as invariably showing a normal sinus rhythm.

Our conception as to the mechanism producing acute pulmonary congestion differs from those given above. We believe that when the heart is speeded up by effort, excitement, or paroxysmal tachycardia, the strong enlarged right ventricle of these hearts with mitral stenosis but without heart failure expels more blood into the pulmonary circulation than can be passed through the stenosed mitral valve in the same unit of time. Cardiac asthma may or may not appear at this time; the process may proceed to excessive formation of edema giving moist râles, to frank hemoptysis, and even to death. This theory is in accord with the ideas of Wenckebach, Shellong, and Thums, who have considered the importance of the hyperactivity of the right ventricle in such cases. Failure of the right ventricle may occur secondarily, with a consequent tricuspid insufficiency and a backing up of

the blood peripherally into the neck veins and into the liver, with relief of the intense pulmonary congestion. An alternative, less plausible, explanation of acute pulmonary congestion with mitral stenosis is that the left ventricle in such cases, small or of normal size and unaccustomed to expel much blood because of its underfilling resulting from the obstruction due to the marked mitral stenosis, fails abruptly when it is suddenly supplied with an increased volume of blood, the surplus remaining behind to cause the pulmonary congestion. If, however, the mitral stenosis is of sufficient degree in these cases to prevent an adequate amount of blood from entering the left ventricle at ordinary heart rates, it is extremely unlikely that this same obstruction will fail to protect the left ventricle from any gross oversupply of blood when the heart is beating rapidly. The left ventricle in such cases should, like the left ventricle in the normal heart, be able to deal with the increase in blood supplied to it at increased heart rates, since the left ventricle itself is not diseased (as indicated by the post-mortem examinations of the three cases referred to above) and since the extra volume of blood will not be as great as that which would result from tachycardia in a heart without the obstruction of mitral stenosis. The normal left ventricle does not fail when it is temporarily given more blood during tachycardia.

In cases of mitral stenosis associated with an enlarged and dilated left ventricle due to systemic hypertension or to an aortic valve lesion, we may assume that either or both of the above described mechanisms causing acute pulmonary vascular congestion may be effective. A patient having such lesions may have attacks of acute pulmonary congestion with hemoptysis following exertion at an early stage and later have similar attacks with frothy sputum rather than hemoptysis coming on while at rest, especially in sleep (we have noted three such cases).

SUMMARY

We have made a study of 20 cases of mitral stenosis with attacks of acute pulmonary congestion with or without cardiac asthma; 10 were uncomplicated and 10 were complicated by factors (aortic valve disease or hypertension) causing strain on the left ventricle. We have compared the findings in these groups with those in a group of much more common cases, namely, those of acute pulmonary vascular congestion with cardiac asthma without mitral stenosis. Three of the 10 cases with uncomplicated mitral stenosis were examined after death.

In the large group of cases with left ventricular strain and failure, acute pulmonary congestion is found in older persons, comes on most often while the patient is at rest, has a poor prognosis, but may be successfully treated for a while with digitalis and diuretics. Here the

acute pulmonary congestion evidently results from a backing up of blood in the pulmonary vessels due to the inability of the left ventricle to expel its full contents.

In the small group of cases of uncomplicated mitral stenosis, acute pulmonary congestion is observed in younger patients; the attacks are precipitated by exertion or paroxysmal tachycardia and are often accompanied by frank hemoptysis; the prognosis is more favorable than in most other cases of cardiac asthma, although digitalis and diuretics are of less value. Here the best explanation of the acute pulmonary congestion is that when the heart is stimulated to greater work, the hypertrophied and dilated right ventricle propels more blood into the pulmonary vessels than can pass through the stenosed mitral valve in the same unit of time, with a consequent acute pulmonary congestion.

The case reports upon which this study is based will be published with the reprints of this article. Reprints may be obtained from the authors on request.

REFERENCES

1. McGinn, S., and White, P. D.: A Follow-Up Report on the Clinical Study of Two Hundred and Fifty Cases of Cardiac Asthma and a Survey of an Additional Group of Twenty-Two New Cases, *New England J. Med.* 207: 1069, 1932.
2. Merklen, P.: *Leçons sur les troubles fonctionels du coeur.* 1908.
3. Riesman, D.: Acute Pulmonary Edema With Special Reference to a Recurrent Form, *Am. J. M. Sc.* 160: 88, 1907.
4. Vaquez, H., translated by Laidlaw, G. F.: *Diseases of the Heart*, Philadelphia and London, 1924, p. 607, W. B. Saunders Co.
5. Robinson, G. C.: *Nelson's Loose Leaf Medicine*, Thomas Nelson and Sons, vol. IV: 509, 1920.
6. Gallavardin, L.: De l'oedeme pulmonaire aigu dans les cardiopathies valvulaires endocardiques en dehors de la gravidité insuffisance ventriculaire et insuffisance auriculaire gauches, *Arch. d. mal du coeur* 14: 262, 1921.
7. Saloz, C., and Frommel, E.: Oedeme pulmonaire et stenose mitrale, *Arch. d. mal du coeur* 16: 570, 1923.
8. Thums, K.: Akutes Lungenödem bei Mitralstenose, *Klin. Wchnschr.* 12: 1644, 1933.
9. Henderson, Y., and Prince, A. L.: The Relative Systolic Discharges of the Right and Left Ventricles and Their Bearing on Pulmonary Congestion and Depletion, *Heart* 5: 217, 1914.
10. Oppenheimer, B. S., and Schwartz, S. P.: Paroxysmal Pulmonary Hemorrhages. The Syndrome in Young Adults With Mitral Stenosis, *AM. HEART J.* 9: 14, 1933.

HUGE T-WAVES IN PRECORDIAL LEADS IN CARDIAC INFARCTION*

FRANCIS CLARK WOOD, M.D., AND CHARLES CHRISTIAN WOLFERTH, M.D.
PHILADELPHIA, PA.

THE electrocardiographic study of acute coronary occlusion with chest leads is bringing to light certain new features. One of the phenomena which has interested us recently is the occurrence of huge T-waves in precordial leads in this disease.^{1, 2} The present paper is a report of seven cases showing this finding.

Six of the seven cases showed huge upright T-waves in Leads IV or V,[†] which exceeded 13 mm. in amplitude. One case showed a very large inverted T-wave in Lead V, 19 mm. deep. The electrocardiographic string deflection was standardized carefully in each instance, and skin resistance was kept low, so that no "overshooting" occurred. Therefore we feel confident that this electrocardiographic phenomenon cannot be attributed to an artefact.

The occurrence of large T-waves in limb leads in coronary occlusion has been noted by several observers, among others Levine and Brown,³ Katz and Bohning,⁴ and Cooksey.⁵ In some cases these waves have a quite distinctive appearance. In others, they look like large normal T-waves.

The huge inverted T-waves which appear in Lead V of Case 7 do not differ greatly from those seen in certain patients without coronary occlusion. We have seen a T-wave in Lead V, 13 mm. deep in a presumably normal college student.⁶ However, when these huge waves are upright in direction (Cases 1 to 6) they present an appearance which differs distinctly from anything we have seen in a series of 550 controls.[‡] We therefore consider the huge upright T-wave in Lead IV or V an important diagnostic feature of acute or subacute cardiac infarction.

Fairly large upright T-waves often appear in precordial leads during the healing of an anterior cardiac infarct.¹ However, among a group of 78 patients with acute coronary occlusion, which has been studied with chest leads,⁷ these 6 are the only cases in which the T-wave in Lead IV or V has exceeded 10 mm. in height.

*From the Edward B. Robinette Foundation, Medical Division, Hospital of the University of Pennsylvania.

†The various chest leads are designated by the numbers IV, V and VI as in a previous communication.¹

‡The controls consist of 200 patients with various types of cardiovascular disease, and 350 patients in whom no evidence of heart disease could be elicited. Two hundred and fifty of the latter are college students.⁶

CASE REPORTS

CASE 1.—W. S., a man of fifty-seven years, was well until Sept. 28, 1932. That morning at 9 A.M., as he was walking out of his front door preparing to go to work, he was seized with a "terrible" pain across the left side of the chest in the region of the nipple. He went to bed, took some hot water, and in fifteen minutes the pain began to abate. As he started downstairs once more, he experienced another similar attack. He lay down and took some more hot water. In twenty minutes this attack subsided, but a soreness persisted in his chest for an hour longer. He then went to work on his butter and egg route. At 3:30 P.M. the pain began again. He went home and after an hour this third attack wore

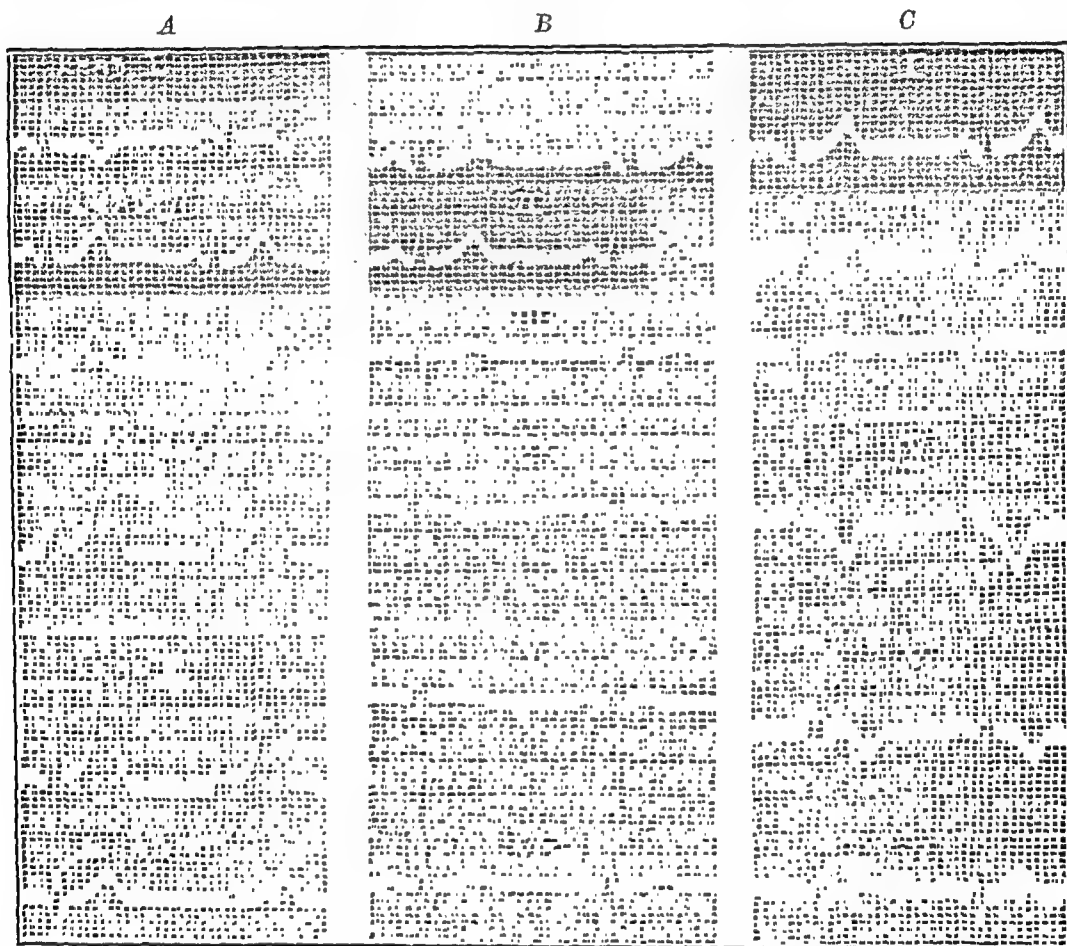


Fig. 1.—Electrocardiograms of Case 1. The various chest leads are designated by numbers IV, V, and VI as in a previous communication.¹ The anterior electrode in Leads IV and V was placed in the fourth left interspace, 4 cm. from the sternum.

A, Tracing taken on Nov. 3, 1932, five weeks after the onset. T_1 is inverted, T_2 and T_3 are quite large. T_4 is +13 mm. T_5 is +22 mm. The QRS complex in Leads IV and V is M-shaped, resulting from small upward deflection, preceding the initial downward deflection. The RS-T interval is slightly elevated in Leads IV and V. No other chest leads were taken on this date.

B, Tracing taken on April 17, 1933, seven and a half months after the onset. The QRS complexes are somewhat similar to those of Nov. 3. The T-waves have changed markedly. The huge T-waves in Leads IV and V have disappeared and T_1 has become upright. Moving the anterior chest electrode to a point over the apex-impulse caused a slight reduction in size of the initial upward deflection of QRS in Leads IV and V, but did not change the T-waves.

C, Tracing taken on Dec. 28, 1933. Definite changes are evident. The only abnormalities remaining in the electrocardiogram are a left axis deviation, slight slurring of QRS, especially in Lead II, and an initial upward deflection of QRS in Lead V, 4 mm. high. Moving the anterior chest electrode to the apex and beyond caused the initial upward deflection of QRS to disappear, but did not alter the T-waves.

off. The next day he went to work and has continued his occupation since that time. He says, however, that he felt "washed out" for two months. After December, 1932, he felt well, except for attacks of intermittent claudication induced by walking seven or eight blocks. These attacks are more marked in the right leg. He was last seen on Dec. 28, 1933. He had experienced a few mild anginal attacks induced by effort, during the preceding month.

This patient first came to the cardiac clinic of the Hospital of the University of Pennsylvania on Oct. 31, 1932, about five weeks after the onset. He was a well-nourished male. The blood pressure was 160 mm. systolic and 95 mm. diastolic. The heart was normal in size and shape (orthodiagram). There were no signs of congestive failure. Auscultation revealed a harsh systolic murmur at the apex, a softer systolic murmur at the base, and an accentuated second sound. The sounds were slightly distant. The blood count and urine analysis showed normal findings (WBC were 7,300). The blood Wassermann reaction was negative. During his last visit on Dec. 28, 1933, the blood pressure was 120 mm. systolic and 85 mm. diastolic. The heart sounds were normal except for a rather rasping reduplication of the first sound at the apex. No other changes were noted in the general physical examination or orthodiagram.

Electrocardiograms (Fig. 1) were taken on Nov. 3, 1932, April 17, 1933, Dec. 28, 1933. The first tracing, five weeks after the onset, showed an inverted T-wave in Lead I and huge T-waves in Leads IV and V. The second tracing showed a disappearance of the huge T-waves and certain other changes in the ventricular complexes. The last tracing showed a normal electrocardiogram except for slurring of the QRS complex in Lead II, left axis deviation, and an upward deflection preceding the downward deflection of QRS in Lead V.

Summary: A fifty-seven-year-old man suffered three severe attacks of precordial pain on Sept. 28, 1932. On Nov. 11 while the patient was still feeling below par, the electrocardiogram showed huge T-waves in Leads IV and V. These large waves disappeared subsequently. The electrocardiogram a year later showed normal T-waves and a few slight abnormalities of QRS.

CASE 2.—W. M. B., whose case has been reported,* was a man of fifty-four years, who had attacks of pain over the heart on Oct. 12 and on Dec. 22, 1932. He died Dec. 30, 1932, in a third severe attack which began on Dec. 28. Necropsy showed an infarct in the anterior surface of the left ventricle. The electrocardiogram on Dec. 24 showed huge T-waves in Leads IV and V, 15 mm. high.

CASE 3.—M. G. was a man of fifty years of age. Since 1929 he had experienced attacks of dull pain in the ulnar side of the left forearm radiating up to the shoulder and to the precordium. The attacks were induced by effort, emotion and the ingestion of food. They were relieved by rest and relaxation. On Feb. 17, 1933, at 7 A.M., shortly after arising from bed, he was seized with a severe agonizing pain in the left forearm, which rapidly extended up the arm and into the precordium. It was partly relieved by morphine after thirty minutes, but it returned and persisted as a rather severe dull ache for twenty-four hours. He was admitted to the Hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel on Feb. 17. The blood pressure was 120 mm. systolic and 80 mm. diastolic. The heart sounds were distant; the left border of the heart was 10 cm. from the midsternal line; there were no signs of congestive failure. The next day, fever (102° F.) and leucocytosis (12,300) appeared. Slight fever

*See Reference 1, Case 19, Chart 4.

persisted for ten days. The leucocyte count reached 20,000 on Feb. 19 and subsided to normal on Feb. 27. The blood pressure dropped to 100 mm. systolic and 70 mm. diastolic on Feb. 19, and a few râles appeared at the right base. He gradually improved and was discharged on April 8. During his stay in the hospital he suffered frequent attacks of moderately severe aching pain in the region of the left elbow, every day or two, for six weeks. The most severe attack occurred on March 16 and lasted several hours. No pain was felt in the precordium after the first twenty-four hours of hospitalization. On Feb. 18 urinary retention necessitated catheterization. This was followed by a relatively mild urinary tract in-

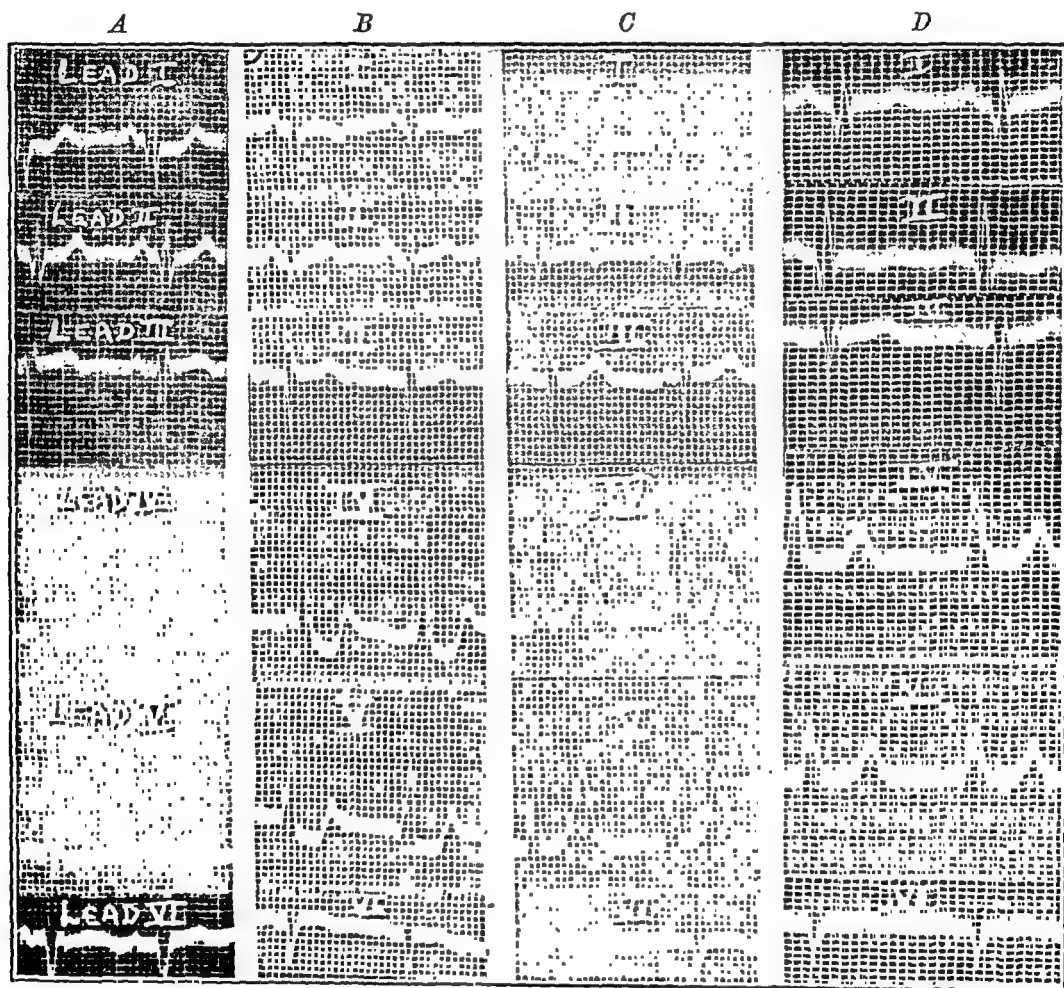


Fig. 2.—Electrocardiograms of Case 3. The patient had an attack of probable coronary occlusion on Feb. 17, 1933, beginning at 7 A.M. The chest leads in this figure were taken with the anterior electrode at the apex impulse, and the posterior electrode in the usual position at the angle of the left scapula.

A, Tracing taken on Feb. 17 at 5 P.M. The RS-T interval is slightly depressed in Lead I. QRS₁ and QRS₂ are somewhat M-shaped. No RS-T interval deviations could be elicited in the chest leads, although the anterior electrode was moved to various positions on the precordium and beyond the apex impulse.

B, Tracing taken on Feb. 20. The typical signs of an acute anterior infarction are present. T₁ is inverted. The initial downward deflection of QRS in Leads IV and V is absent. The RS-T interval in Leads IV and V is depressed below the isoelectric line. The T-wave in these leads is beginning to turn upward. No other chest leads were taken.

C, Tracing taken on March 28. T₁ is deeply inverted. The initial downward deflection of QRS in Leads IV and V is absent. T₁ is +14 mm. T₂ is +12 mm. No other chest leads were taken.

D, Tracing taken on Jan. 6, 1934. The signs of an old anterior infarct are still present. Other tracings taken with the anterior electrode on the fourth left rib, 4 cm. from the sternum showed an M-shaped QRS complex, but no difference in T-waves. (The tracing labelled "Lead I" is Lead II, and vice versa.)

fection. On March 23 he suffered a right brachial embolus, the symptoms of which were not particularly disturbing.

After discharge on April 8 he lived a fairly restricted life and felt quite comfortable. When last seen Jan. 6, 1934, he was working as a tailor. His attacks of effort angina had become more frequent, and more readily induced since November, 1933. The blood pressure was 140 mm. systolic and 80 mm. diastolic. There was moderate enlargement of the heart (orthodiagram). There were no signs of congestive failure, and no significant murmurs; the heart sounds were distant.

Repeated electrocardiograms were taken (Fig. 2). The first, on the day of onset (Feb. 17, 1933) showed no very definite RS-T interval deviations. The main abnormality was an absence of the initial downward deflection of QRS in Lead IV; the T-waves were upright in the limb leads and not large. On Feb. 20, T_1 was inverted (-1 mm.); and Lead IV showed the signs of recent infarction in the anterior surface of the left ventricle.¹ On Feb. 28, T_1 was more deeply inverted (-3 mm.) and T_4 was 6 mm. high. On March 6, T_1 was still -3 mm. and T_4 was $+10$ mm. On March 16, T_1 was -4 mm. and T_4 was $+14$ mm. On March 28, T_1 was -3 mm., T_4 was $+14$ mm. On Jan. 6, 1934, the signs of an old infarct in the anterior surface of the left ventricle were still present; T_1 was $+4$ mm. and Q_4 was absent. From results which we have obtained in subsequent patients, we are inclined to believe that a much larger upright T-wave in Lead IV might have been obtained on Feb. 28 and thereafter, by varying the position of the anterior chest electrode. (See Fig. 6.)

It is not entirely clear in this case, how much of the fever and leucocytosis was due to the urinary tract infection. Nevertheless, there is little doubt that the patient suffered a coronary occlusion, possibly a slowly developing occlusion, beginning on the morning of Feb. 17, 1933.

Summary: A fifty-year-old man, who had previously suffered from effort angina, developed the symptoms and signs of a coronary occlusion on Feb. 17, 1933. Huge upright T-waves appeared in Lead IV, several weeks after the onset, and disappeared subsequently.

CASE 4.—S. B., a woman of sixty-five years, had been known to have a blood pressure exceeding 200 mm. systolic and 100 mm. diastolic for at least seven months prior to her present illness. She had suffered a few mild anginal pains during this seven months' period. On March 11, 1933, she was admitted to the Hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel. That morning, without warning, the patient had suffered a severe attack of pain over the heart and in the left hypochondrium, referred to the left shoulder and arm. Both arms felt numb. Extreme weakness, trembling and profuse perspiration occurred, and the patient felt very cold and faint. On admission, the blood pressure was 140 mm. systolic and 70 mm. diastolic. The heart sounds were distant, gallop rhythm was heard at the apex, and occasional extrasystoles were noted. There was slight dyspnea, some pallor, and moist coldness of the skin. The lips were slightly cyanosed. Râles were noted at the lung bases. The acute pain persisted for eight hours; a residual soreness remained for twenty-four hours. During the first six weeks of her stay in the hospital she suffered repeated attacks of dull pain over the heart and in the left hypochondrium. Fever (100° F.) was present on March 12, and disappeared the next day. Recurrent elevations of temperature appeared between April 5 and 16. She remained afebrile after that time. The only elevated leucocyte count was 11,400 on March 12. The lowest blood pressure recorded was 90 mm. systolic and 60 mm. diastolic on the afternoon of her admission, March 11. It then rose to 110 mm. systolic and 70 mm. diastolic and remained

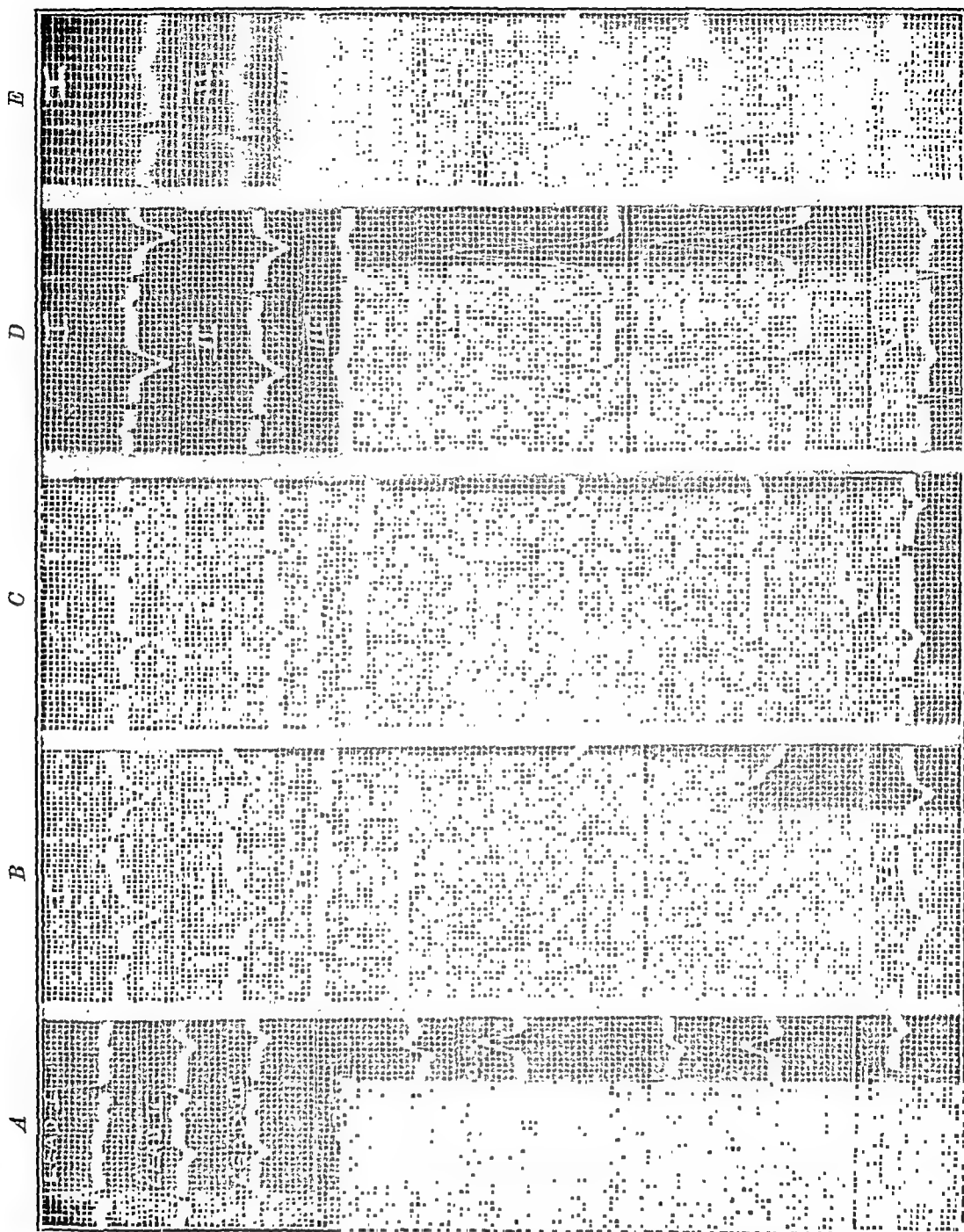


Fig. 3.—Electrocardiograms of Case 4. The patient had an attack of cardiac pain on March 11, 1933. All the tracings in this figure, except when otherwise stated, were taken with the anterior chest electrode at the apex impulse. The largest T-waves were obtained from a point 3 cm. to the left of the apex.

A, Tracing taken March 11. Lead I shows a slight RS-T interval elevation. Lead II shows an inverted T-wave. Lead IV shows a small initial downward deflection of QRS, a slight depression of the RS-T interval, and a diphasic T-wave. Lead V shows an M-shaped QRS complex. Leads IV *a* and V *a* were taken with the anterior electrode 4 cm. to the left of the apex impulse. They show marked differences from Leads IV and V, which were taken from the apex.

B, Tracing taken March 13. Large inverted T-waves have appeared in Leads I and II. Huge upright T-waves are present in Leads IV and V, 24 mm. and 18 mm. high. T₀ has become quite deeply inverted. The RS-T interval in Leads IV and V is slightly elevated.

C, Tracing taken March 20. All the T-waves are smaller.

D, Tracing taken April 10. All the T-waves have become large once more, resembling those on March 13. By May 16 the T-wave had again become quite small.

E, Tracing taken Jan. 6, 1934. Left axis deviation is the only abnormality which has persisted.

below 160 mm. systolic throughout her hospital stay. She was last seen on Jan. 6, 1934. The blood pressure at that time was 220 mm. systolic and 80 mm. diastolic. She was still experiencing mild anginal pain from time to time but was quite comfortable on a limited schedule of activity.

Many electrocardiograms were taken (Fig. 3) March 11, 12, 13, 15, 20, 28, April 10, 20, May 4, 16, 1933, and Jan. 6, 1934. On the first day the tracings varied considerably, depending upon the position of the anterior electrode on the chest, but the T-waves were not especially large. Slight RS-T interval deviations appeared in Leads IV and V. On March 12, the tracing had changed markedly. Huge upright T-waves had appeared in Lead IV, 18 mm. high, which were largest with the anterior electrode placed just to the left of the apex. On March 13, T_1 reached 24 mm. in height. On March 20, it was smaller; on March 28, again somewhat larger. On April 10, it was again huge (25 mm. high). It then gradually became smaller until on May 16, just before discharge, it was no more than 5 mm. in height. The final tracing, taken on Jan. 6, 1934, was practically normal in all leads except for left axis deviation.

Summary: A woman of sixty-five years experienced severe pain over the heart on March 11, 1933. Huge T-waves appeared in Lead IV on March 12 and persisted more or less for five weeks. The tracing at present, Jan. 6, 1934, is normal except for left axis deviation.

CASE 5.—Mrs. R. B. was a mildly diabetic woman of sixty-three years, who was admitted to the Hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel on July 26, 1933. She was thought to be suffering from cholelithiasis on account of severe epigastric pain radiating to the back, and on account of the finding of a large gall stone by x-ray examination, "probably impacted in the cystic duct." However when an electrocardiogram was taken on July 29, a review of her history elicited the following facts: Since the first of June, 1933, she had suffered attacks of pain in the left side of the epigastrium, radiating to the region of the fourth dorsal vertebra. These attacks were induced by effort, and relieved by rest. On July 15 she had a severe attack of pain in the same regions, not induced by effort, lasting two hours. On July 24 another prolonged seizure took place. On July 27 the third attack occurred, while she was in the hospital. It lasted three hours and required morphine (gr. $\frac{1}{2}$) for relief.

On admission, July 26, the blood pressure was 190 mm. systolic and 90 mm. diastolic. There was moderate cardiac enlargement (orthodiagram). No murmurs were heard. No signs of congestive failure were observed. On July 27 cyanosis of the lips and extrasystoles were noted. Slight fever appeared (100° F.) and persisted for three days. On July 29 the blood pressure was 90 mm. systolic and 60 mm. diastolic, and a few basal râles were heard. The leucocytes were not counted during the febrile period. Before and after this period they were within normal limits. The blood pressure varied between 120 mm. and 160 mm. systolic and 80 mm. to 90 mm. diastolic for the next week; then it became stabilized more or less in the vicinity of 160 mm. systolic and 80 mm. diastolic. The patient was discharged Aug. 28 to return to her home for further convalescence. During September she had another attack of probable coronary occlusion. On Oct. 20 she died at home in an attack, more severe and more prolonged than any previous seizure. Permission for necropsy was not obtained.

Electrocardiograms were taken on July 29, 31, Aug. 7, 16, 28 (Fig. 4). On July 29 Lead IV showed a T-wave 15 mm. high. By July 31 the T-waves in the limb leads had become much smaller, and T_1 was only 6 mm. high. Large T-waves in Lead IV were not seen in any subsequent tracing.

Summary: A mildly diabetic woman of sixty-three years suffered severe attacks of pain in the left hypochondrium on July 15, 24, and 27, 1933. The electrocardiogram changed rapidly from day to day, after it was first taken on July 29. Huge T-waves were present in Lead IV on July 29 and disappeared shortly afterward. The patient died Oct. 20, 1933, presumably of coronary occlusion.

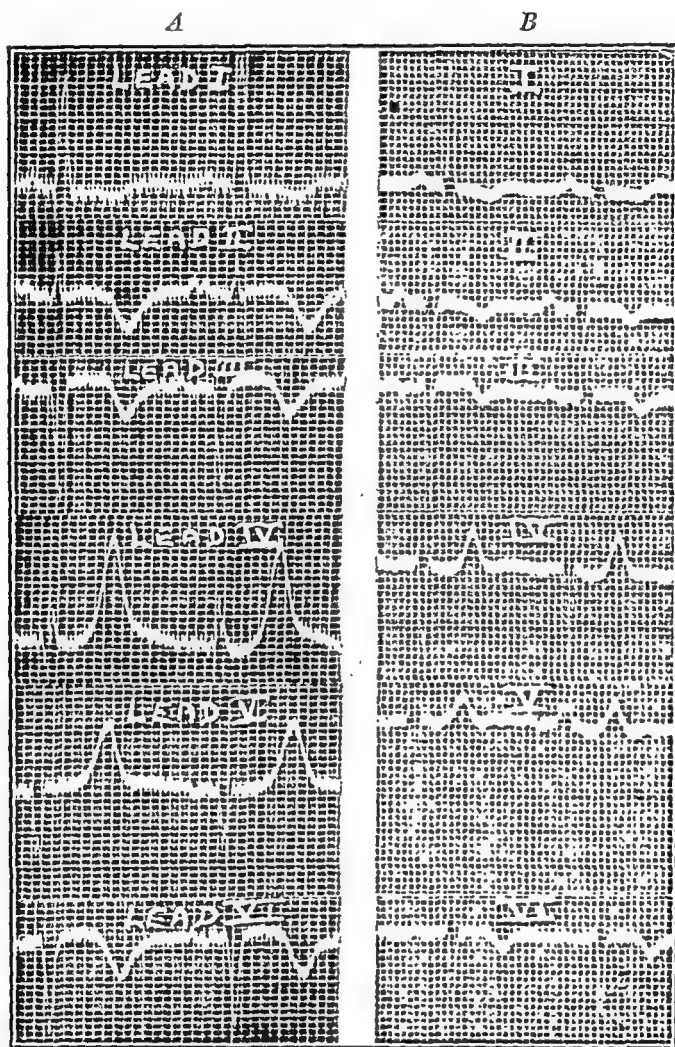


Fig. 4.—Electrocardiograms of Case 5. The patient suffered attacks of cardiac pain on July 15, 24, and 27, 1933. All chest leads were taken with the anterior electrode at the apex impulse. No other chest leads were taken in this case.

A, Tracing on July 29, two days after the last attack of pain. T_1 is diphasic. T_2 and T_3 are deeply inverted. T_4 is +15 mm. T_5 is +9 mm. T_6 is deeply inverted. The QRS complexes in Leads IV and V are quite different. The RS-T interval is practically on the isoelectric line.

B, Tracing taken July 31. The large T-waves in all leads have disappeared. QRS₄ has changed its direction. T_4 and T_5 are still upright but much smaller.

CASE 6.—M. W. was a man of fifty-six years. He began to have attacks of severe pain in the lower sternal region on Nov. 1, 1933. The seizures were usually related to eating. They began as a drawing sensation which soon developed into a severe viselike constriction, lasting as a rule about thirty minutes. He had six such attacks during November. He was hospitalized at the Mount Sinai Hospital on Nov. 27, but signed his release on Dec. 10 because he felt well and had experienced only two mild attacks during his two weeks' stay in the hospital. On Dec. 12, he had the most severe seizure of all, during which he coughed up some blood-streaked sputum. Three doses of morphine (amount unknown) were required

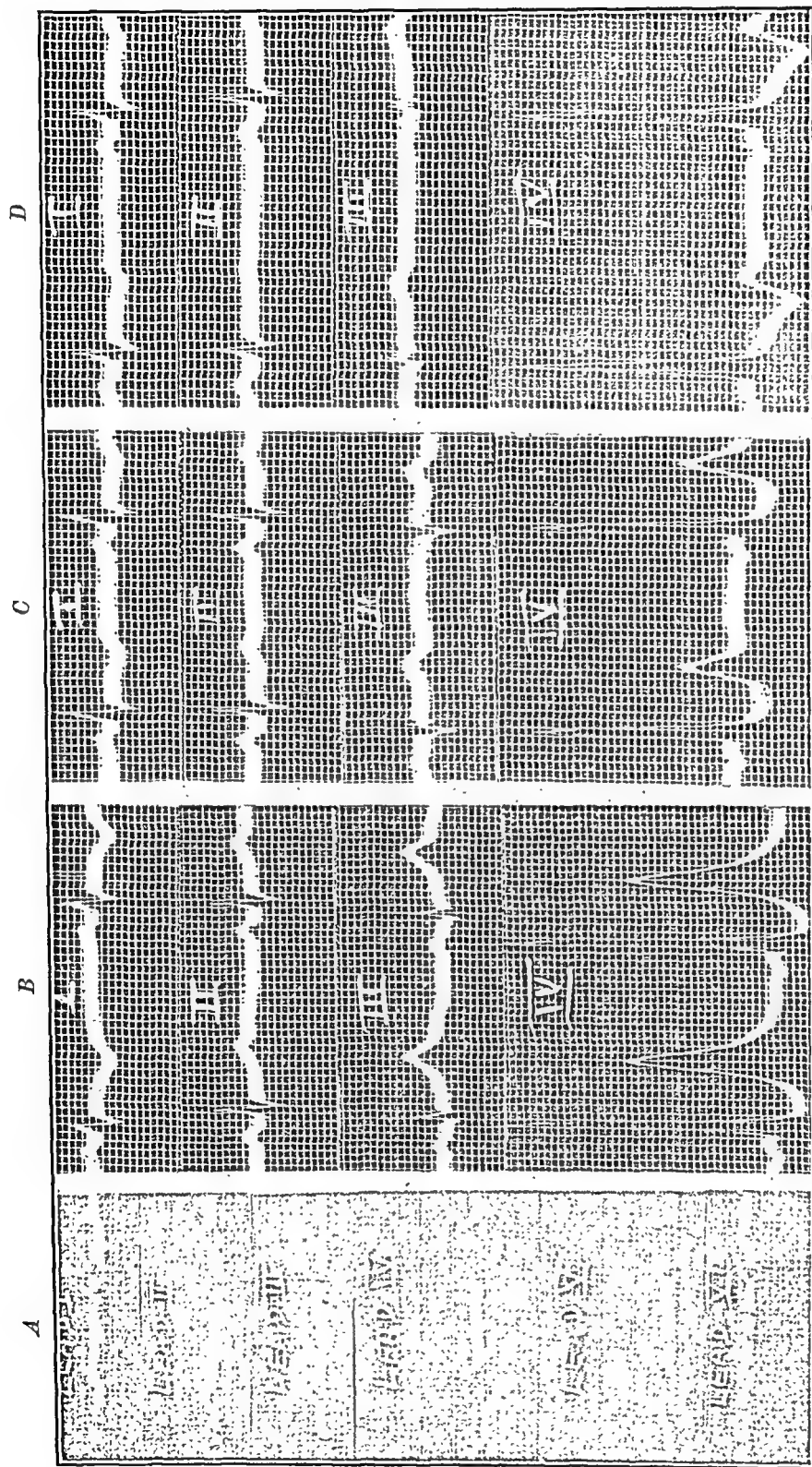


Fig. 5.—Electrocardiograms of Case 6. This patient suffered repeated attacks of cardiac pain. The most severe seizure occurred on Dec. 12, 1933. The tracings shown in this figure were taken with the anterior chest electrode on the fourth rib, 4 cm. to the left of the sternum. The deflections were much larger from this point than from any other on the precordium. (See Fig. 6.) Lead V in this patient was practically identical with Lead IV in B, C and D; consequently it has been omitted from this figure.

A, Tracing taken Dec. 6, given to us by Dr. Joseph Edelken. T_1 is slightly inverted. T_2 and T_3 are normal. The initial downward deflection in Leads IV and V is absent. T_1 and T_3 are diphasic. There is a slight depression of the RS-T interval, especially in Lead IV.

B, Tracing taken Dec. 12. T_1 is definitely inverted. T_3 is quite large. Lead IV shows a huge T-wave, 20 mm. high. The initial downward deflection of QRS is absent. The RS-T interval is depressed below the isoelectric line.

C, Tracing taken Dec. 15. T_1 is diphasic. T_3 has become smaller. The T-wave in Lead IV has become much smaller.

D, Tracing taken Jan. 22. The limb leads have not changed very much since Dec. 15. T_1 is diphasic.

to relieve the pain. He was admitted to the hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel on the day of this last attack. The only other noteworthy features of his past history were the use of alcohol daily (8 oz.) for some years, and attacks of intermittent claudication in the left leg since 1925.

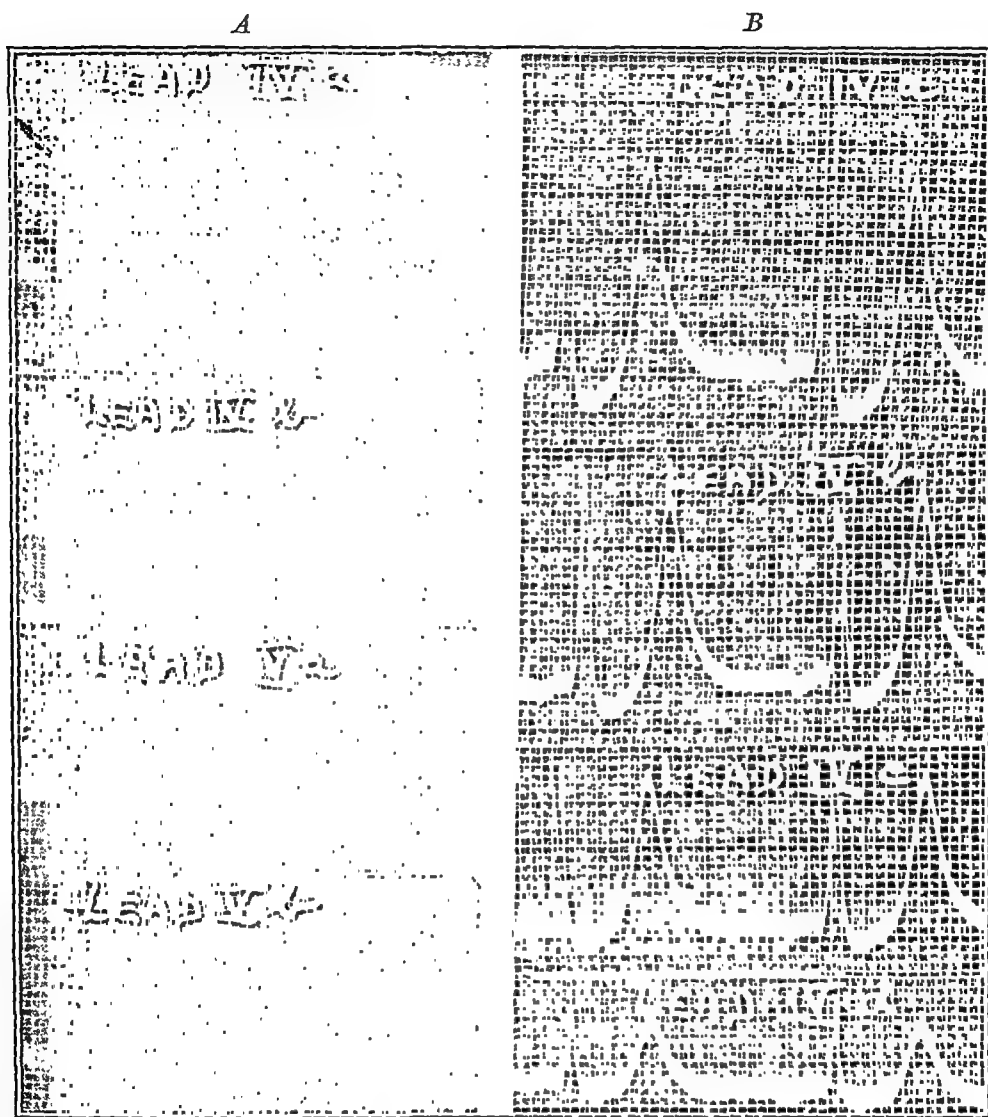


Fig. 6.—Electrocardiograms of Cases 4 and 6, showing the marked differences produced in the chest lead tracings by varying the position of the anterior chest electrode.

A, Electrocardiograms of Case 4, taken March 12. *IV a* is Lead IV with the anterior chest electrode on the fourth rib 4 cm. to the left of the sternum. *IV b* is Lead IV with the anterior electrode 3 cm. to the left of the apex impulse. *V a* and *V b* are Lead V taken with the anterior electrode in the same positions as in taking *IV a* and *IV b*. Marked differences were produced, both in the QRS complexes and the T-waves, by moving the position of the anterior electrode. In this case the "huge" T-waves were obtained from a point 3 cm. to the left of the apex impulse. They were not seen when the anterior electrode was placed on the fourth rib, 4 cm. to the left of the sternum.

B, Electrocardiograms of Case 6 taken Dec. 12. All the tracings were taken with Lead IV, the anteroposterior chest lead. Since Lead V was almost identical, it has been omitted from this figure. *a*, Anterior electrode on the fourth rib, 4 cm. to the left of the sternum; *b*, anterior electrode at the apex impulse; *c*, anterior electrode 4 cm. above the apex impulse; *d*, anterior electrode 4 cm. to the left of the apex impulse.

Case 6 differs from Case 4 in that the T-waves were the largest when the anterior electrode was placed over the fourth rib, 4 cm. to the left of the sternum. They were the smallest when the anterior electrode was placed 4 cm. to the left of the apex impulse.

On admission the patient showed slight cyanosis of the lips. The temperature, pulse, and respirations were normal. There was a difference of blood pressure in the two arms, the right being 74 mm. systolic and 62 mm. diastolic, and the left 142 mm. systolic and 68 mm. diastolic. No pulses could be felt in the arteries of the feet. The lower extremities were cold. The heart sounds were not particularly abnormal. There was no demonstrable enlargement of the heart. A few râles were heard at the left base. A tentative diagnosis of coronary occlusion and Buerger's disease was made.

On Dec. 15, 1933, the temperature reached 99° F. on two occasions. On Dec. 23 it reached 100° F. At other times it has been normal. The leucocyte count reached 12,000 on Dec. 18, 1933, on Jan. 2 and 15, 1934. At other times it has varied from 7,000 to 10,000. Despite continued rest in bed the patient suffered repeated attacks of severe substernal pain every two or three days from the time of admission until Jan. 17. On that day he had a seizure lasting three hours. Since then he has been free from pain. These attacks have been associated with an elevation of the blood pressure from its usual level of 130 mm. systolic and 70 mm. diastolic, to 170 mm. to 180 mm. systolic and 90 mm. to 110 mm. diastolic. Electrocardiographic changes were noted during the last paroxysm, which disappeared after the pain had subsided. Morphine was usually necessary during the attacks. Nitroglycerin gave no relief.

The electrocardiograms are shown in Fig. 5. The first tracing, obtained from Dr. Joseph Edeiken, taken on Dec. 6, showed evidence suggesting a healing infarct in the anterior surface of the left ventricle. The second tracing (Dec. 12) showed huge T-waves in Lead IV, 20 mm. high. By Dec. 15 the huge T-waves had disappeared and certain changes had occurred in the limb leads. Tracings on Dec. 18, and 21, 1933, and Jan. 17, 22, and 26, 1934, have not shown huge T-waves.

Summary: A man of fifty-six years with probable thromboangiitis obliterans suffered recurring pains over the heart, beginning on Nov. 1, 1933. After a very severe attack on Dec. 12 he was brought to the hospital. On that day the T-waves in Lead IV were 20 mm. high. Three days later the huge T-waves had disappeared.

CASE 7.—S. B. was a man of fifty-three years who had been well until Sept. 15, 1933. On that day while working as a "mattress maker," he noticed a heavy aching discomfort in both wrists, and a "queer" indescribable sensation in the lower substernal region. He sat down and the discomfort passed off in about an hour, leaving no noticeable after-effects. The next day at 11 A.M., he noticed a queer "jumping feeling" near the xiphoid. Soon the same heavy ache appeared in both wrists, and a severe pain developed in the lower sternal region. He felt weak, faint, and dizzy. The severe pain lasted two hours. After that it recurred each time he made the least physical effort. He did not go to bed. Since then he has had substernal pain on moderate effort, relieved by rest.

He was studied at the Mount Sinai Hospital from Oct. 25 to Dec. 7, 1933, on the service of Dr. Rubenstone. He had no fever, no leucocytosis, no abnormalities of heart sounds, and no evidence of congestive failure. The blood pressure was 125 mm. systolic and 70 mm. diastolic. A tonsillectomy was performed on Dec. 1, 1933.

He was seen by us on Jan. 27, 1934, through the kindness of Dr. Joseph Edeiken. His exercise tolerance had improved so that he could walk three blocks. The substernal pain induced by effort radiated to the right side of the chest and right shoulder, rather than to the left. The blood pressure was 130 mm. systolic and 80 mm. diastolic. There were no new physical signs. The orthodiagram showed slight enlargement of the left ventricle.

The electrocardiograms are shown in Fig. 7. The first tracing taken at Mount Sinai Hospital on Oct. 30, 1933, shows deeply inverted T-waves in Leads II and III. Lead IV shows a T-wave of normal size (~ 10 mm.). Lead V shows a T-wave of unusually large size (~ 19 mm.). Lead VI is similar to Lead III. The most recent tracing, taken Jan. 27, 1934, shows a disappearance of these large T-waves.

Summary: A man of fifty-three years suffered an attack of substernal pain on Sept. 16, 1933, lasting two hours. From that time on he has had effort angina, induced by slight exertion. On Oct. 30 an electrocardiogram showed T-waves in Lead V, 19 mm. deep, which returned to normal at a later date. In this case, the

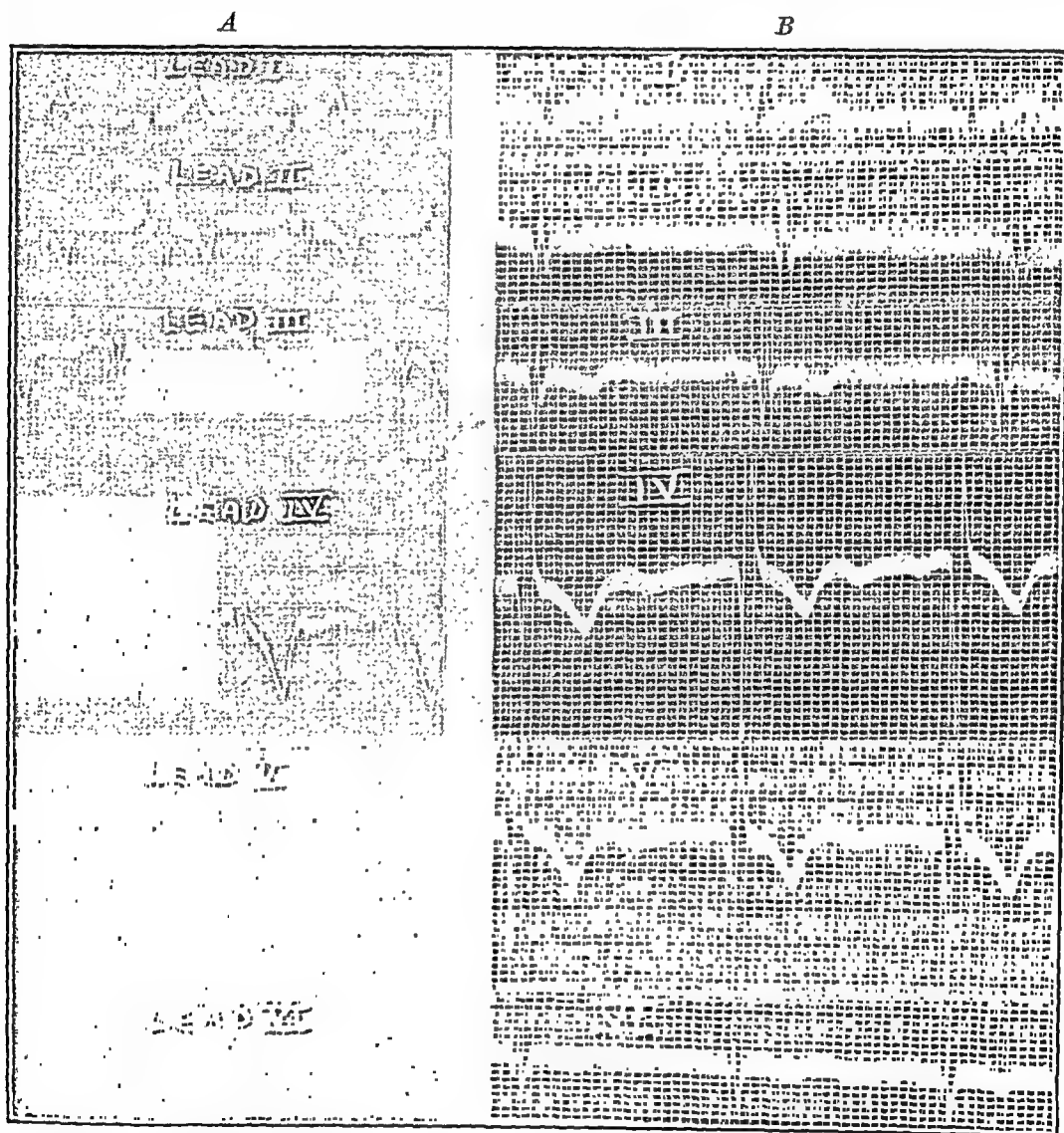


Fig. 7.—Electrocardiograms of Case 7. A moderately severe attack of substernal pain occurred Sept. 16, 1933. Since then the patient suffered recurring attacks of effort angina. Leads IV and V were taken with the anterior chest electrode at the apex impulse.

A, Tracing taken Oct. 30, six weeks after the onset. Lead I shows a large normal T-wave. Leads II and III show deep Q-waves and sharply inverted T-waves. Lead IV is quite normal. Lead V shows a huge inverted T-wave (~ 19 mm.). Lead VI resembles Lead III.

B, Tracing taken Jan. 27, 1934. The abnormally large T-waves have disappeared. The Q-waves in Leads II and III have persisted. T₂ is flat. Otherwise the tracing appears quite normal.

A T-wave in Lead V of ~ 13 mm. has been seen in a presumably normal student. Consequently the large inverted T-wave in this case cannot be considered so distinctive as the large upright T-waves in Cases 1 to 6.

depth of the T-wave in Lead V is not necessarily diagnostic, though it does exceed any we have seen in normal individuals. However, the history, the changing electrocardiogram, and the characteristics of the limb lead tracings provide fairly good evidence of acute or subacute cardiac infarction.

DISCUSSION

Most of these cases with huge T-waves in Leads IV and V show T-waves of large amplitude in the limb leads. In certain cases, however, we have seen large T-waves in the limb leads without huge T-waves in Lead IV. This may have been due in some instances to the fact that the size of the T-wave in Lead IV varies markedly with the position of the anterior electrode in this group of cases. In Case 4, on Dec. 12, 1933 (Fig. 6 A), the T-wave in Lead IV was 18 mm. high when the anterior electrode was placed 4 cm. to the left of the apex impulse; yet it was only 5 mm. in amplitude, when this electrode was placed on the fourth left costal cartilage, 3 cm. from the sternum. In Case 6 on Dec. 12, 1933 (Fig. 6 B), T_4 was 20 mm. high with the anterior electrode in the third interspace, 4 cm. from the sternum; whereas it was only 8 mm. high with the anterior electrode 3 cm. to the left of the apex impulse. Therefore, it seems likely that huge T-waves might have been recorded in precordial leads of other cases showing large T-waves in the conventional leads, had the anterior electrode been placed in the position most favorable for recording this electrical disturbance. It seems probable that this "most favorable position" varies with the location of the infarct. The variation which occurs in the T-waves in precordial leads with variation in position of the anterior electrode, makes it important to interpret conservatively any changes which appear from day to day. Such changes might be due to alterations in relative position of the heart and anterior electrode, rather than alterations of the action current of the heart. When attempting to elicit huge T-waves, it is necessary to take the electrocardiogram from several different positions on the anterior wall of the chest.

Wilson and his coworkers⁸ state that "since the anterior surface of the left chest is much closer to the heart than the posterior surface, anterior-posterior leads, used by Wolferth and Wood, are essentially precordial leads in which the indifferent electrode is placed on the back instead of upon the left leg." It would necessarily follow from this statement that Lead IV and Lead V taken without moving the anterior electrode are "essentially" the same. Although they are essentially the same in many individuals, particularly in normal individuals, there are certain cases in which Leads IV and V are quite different in contour. In Fig. 1 A of this paper, $T_4 = +18$ mm., $T_5 = +22$ mm. and $T_6 = +4$ mm. In Fig. 3 B, $T_4 = +24$, $T_5 = +18$, and $T_6 = -5$. In Fig. 4 A, $T_4 = +15$, $T_5 = +9$, and $T_6 = -6$. In Fig. 7 A, $T_4 = -10$, $T_5 = -19$, and $T_6 = -9$. These differences were not due to errors in

standardization of string deflection. In other words, when T_4 and T_6 deviate in opposite directions, T_5 is smaller than T_4 . When T_4 and T_6 deviate in the same direction, T_5 is larger than T_4 . The facts with regard to deviations of the RS-T interval seem to be similar. In a previous paper,¹ Chart 9 B shows a definite difference between the RS-T interval deviations in Leads IV and V, the latter being the larger. In this case RS- T_4 and RS- T_6 are both upright. On the other hand Chart 6 of the same paper shows the reverse relationship; i.e., a smaller RS-T interval deviation in Lead V than in Lead IV when RS- T_4 and RS- T_6 deviate in opposite directions. Therefore, both the RS-T interval and the T-wave appear to follow the same general rule, namely, that the amplitude of the deflection in Lead V seems to be approximately equal to the algebraic sum of the deflections in Leads IV and VI. It would seem, therefore, that although Leads IV and V often resemble one another, they not infrequently show marked differences and cannot be considered as substitutes for each other. Consequently, we are at present combining the technic of Wilson with our own. We are taking chest Leads IV, V, and VI with the anterior electrode at the apex; we then take Leads IV and V from two other points on the precordium, namely, (a) 4 cm. to the left of the apex impulse, and (b) over the body of the heart, 4 cm. to the left of the sternum. The use of this multitude of leads will probably not be found necessary for practical purposes in all cases. However, the tracings obtained are often so different (see Fig. 6) that it seems worth while to take them all for the present, especially in cases of acute coronary occlusion.

The appearance of the QRS complex in Leads IV and V in the group of patients with huge upright T-waves in the precordial leads is not constant. In three cases (2, 3, and 6) the initial downward deflection disappeared, as it frequently does in patients with infarction in the anterior surface of the left ventricle.¹ In the other cases the QRS complexes were bizarre. In four cases (1, 2, 3, and 4) at some time during their course a small upward deflection appeared before the initial downward deflection, giving a more or less M-shaped QRS. In a group of 250 presumably normal college students studied as a control series, only two showed a small upward deflection of QRS in Lead IV, prior to the downward deflection.⁶ In neither of these was the deflection more than 1 mm. in amplitude. We therefore believe that a deflection of this type exceeding 2 mm. in height is a distinctly abnormal finding. It is seen most frequently in patients who have a history pointing to previous coronary occlusion. In some cases it seems to be a transition stage in the disappearance, or in the return of the initial downward deflection in Leads IV and V (cf., Case 2). The electrocardiogram of Case 1, taken thirteen months after the attack, was practically normal except for the presence of this wave.

At the time when huge upright T-waves appeared in Lead IV, three cases (2, 3, and 5) showed no deviation of the RS-T interval from the isoelectric line, one case (6) showed a depression of this interval, and two cases (1 and 4) showed an elevation.

The appearance time of these bizarre T-waves was not constant. They appeared in Case 6 on the day of the attack. On the other hand, they were absent in some cases (3 and 4) on the day of the attack, and appeared days or weeks later. Their time of disappearance also varied considerably. In Cases 2, 5, and 6, they disappeared rapidly within two or three days. However, in Case 4, they persisted for five or six weeks and disappeared after that time.

Although the patients in this group present the clinical picture of coronary occlusion, the symptoms and signs immediately associated with the huge T-waves are likely to be less severe than those recorded in the classical textbook description of this disease. Some of the patients have shown only slight fever and leucocytosis, and little or no fall of blood pressure. Two patients have died (Cases 2 and 5). In each instance, death occurred in a subsequent classical attack. In this connection Cooksey's observations⁵ are of interest. He states that his cases with large T-waves in limb leads were suspected of having relatively small infarcts.

A rather striking clinical characteristic of this group of cases seems to be a liability to frequent recurrences of cardiac pain, for days or even weeks after the onset.

Only one case has come to necropsy (Case 2). In this patient the fatal lesion was a large infarct in the anterior surface of the left ventricle. There were no infarcts elsewhere in the heart. Examination of the coronary arteries suggested that several small coronary twigs in the anterior surface of the heart had been obstructed, prior to the fatal attack. With one exception (Case 5)* all the cases with huge upright T-waves in Leads IV and V presented electrocardiographic features more or less indicative of infarction in the anterior surface of the left ventricle.¹ The electrocardiogram of the case with the huge inverted T-wave in Lead V was the type usually associated with lesions in the posterior surface of the left ventricle.

The clinical picture presented by this group of patients and the changing electrocardiogram indicate that some acute or subacute disturbance of the blood supply of a part of the heart muscle is taking place. The relative mildness of the symptoms suggests that the lesion is either complete occlusion of a small coronary vessel or partial occlusion of a large one. The lesion associated with huge upright T-waves in precordial leads is probably located in the anterior surface of the left ventricle, in the distribution of the left anterior descending coronary artery. The lesion in Case 7, with a large inverted T-wave in Lead V,

*It is possible that this patient had several areas of infarction in the heart.

may have been in the posterior surface of the left ventricle. What the chemical change in the heart muscle may be, which causes this type of electrical response, is not known. Possibly it is a disturbance of the nutrition of the myocardial fibers which has not reached a degree sufficient to cause marked RS-T interval deviations.

SUMMARY

1. Seven cases are reported which show huge T-waves in the precordial leads of the electrocardiogram.

2. In all cases the large waves disappeared at a later date.

3. These huge T-waves are sometimes elicited from a small area of the precordium only. If the anterior electrode is placed elsewhere on the anterior chest wall, they may not appear in the tracing.

4. The symptoms in this group of cases point to the diagnosis of coronary occlusion. Their relative mildness suggests the complete occlusion of a small vessel or the partial occlusion of a large one.

5. The lesion associated with huge upright T-waves in precordial leads is probably located in the anterior surface of the left ventricle. The fact that this electrocardiographic phenomenon has not been seen in a series of 550 controls, makes it seem justifiable to regard it as indicative of an acute or subacute disturbance of the coronary circulation.

6. Large inverted T-waves in precordial leads considerably exceeding the normal amplitude probably signify the presence of a lesion in the posterior surface of the left ventricle, analogous to that causing huge upright T-waves.

7. RS-T interval deviations may be absent in this group of cases.

8. A small upward deflection, prior to the downward deflection of QRS in precordial leads, has been observed in several of these cases. This wave is probably an abnormal finding, if more than 2 mm. in height.

REFERENCES

1. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
2. Wood, Francis Clark: Electrocardiographic Diagnosis of Coronary Occlusion. *Pennsylvania M. J.* 37: 309, 1934.
3. Levine, S. A., and Brown, C. L.: Coronary Thrombosis. Its Various Clinical Features (Figure 42), *Medicine* 8: 245, 1929.
4. Katz, L. N., and Bohning, A.: Unusual Changes in the Electrocardiograms of Patients With Recent Coronary Occlusion, *Am. J. M. Sc.* 186: 39, 1933.
5. Cooksey, W. B.: Discussion of a Paper by Dr. A. R. Barnes Before The Central Society for Clinical Research, *J. A. M. A.* 101: 2148, 1933.
6. Edeiken, J. E., and Wood, F. C.: Unpublished observations.
7. Wolferth, C. C., and Wood, F. C.: Unpublished observations.
8. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L. The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.

Q AND T TYPES OF ELECTROCARDIOGRAMS: THEIR
COMPARATIVE AND COMPLEMENTARY VALUE IN
INDICATING OCCURRENCE OF ACUTE
MYOCARDIAL INFARCTION*

ARLIE R. BARNES, M.D.
ROCHESTER, MINN.

IN 1928, Parkinson and Bedford² reported a remarkable series of electrocardiographic tracings obtained following acute myocardial infarction. They found that the changes in the RS-T segment of the electrocardiogram fell into two groups which they designated as T_1 and T_2 types. Whitten and I¹ had arrived at a similar conclusion, and we accepted their nomenclature. The T_1 type of electrocardiogram is characterized in its earliest development by change of level and contour of the RS-T segment in Leads I and II, and a depression of the S-T interval in Lead III. The R-T interval in Leads I and II, but especially in Lead I, usually is elevated above the isoelectric line. The interval is likely to be convex, dome-shaped, or sloping downward toward the T-wave. Diphasic waves or T-waves of a monophasic type are common in the earliest stages. It is important to note that Leads I and III act conversely, so that elevation of the R-T segment in Lead I is opposed by depression of the S-T segment in Lead III. The changes in Lead II, although less in degree, frequently are seen to be similar to those in Lead I in cases of infarction in the anterior portion of the left ventricle. At a later stage, the monophasic or diphasic type of T-wave in Lead I or Leads I and II is replaced by frank inversion. The fact is noteworthy that, as the T-wave becomes inverted in Lead I, the T-wave in Lead III remains upright and becomes exaggerated and sharply peaked. Of particular significance in the later stages is the fact that the R-T segment arises at the isoelectric level, and often retains the rounded contour in Lead I or Leads I and II preceding the inverted T-wave. Pitfalls of interpretation will be avoided if one does not interpret RS-T segments in Lead I, which arise below the isoelectric level, as evidence of infarction. Conditions producing left ventricular strain are prone to produce a negative T-wave in Lead I with an S-T segment arising below the isoelectric level in the absence of myocardial infarction.

The T_2 pattern is characterized by precisely the opposite type of RS-T changes following acute myocardial infarction. In its early stages, the R-T segments are elevated in Leads II and III, and the S-T seg-

*From the Division of Medicine, The Mayo Clinic, Rochester, Minn.

ment is depressed in Lead I. A convex, dome-shaped, or sloping R-T segment preceding the T-wave is observed in Leads II and III. In the later stages, the R-T segment in Leads II and III tends to return to, and eventually reaches, the isoelectric level, and the depressed S-T segment in Lead I disappears. In this stage inversion of the T-wave in Leads II and III, with a rounded contour of the RS-T segment, is observed, whereas the T-wave in Lead I is upright, and becomes exaggerated and sharply peaked. Here again one must insist, in the later stages, that the R-T segment preceding the negative T-waves in Leads II and III arises on the isoelectric line, if the segment contours are to be regarded as evidence of a preceding acute myocardial infarction.

Wilson and his associates³ recently described certain changes in the initial deflections of the ventricular complex in association with myo-

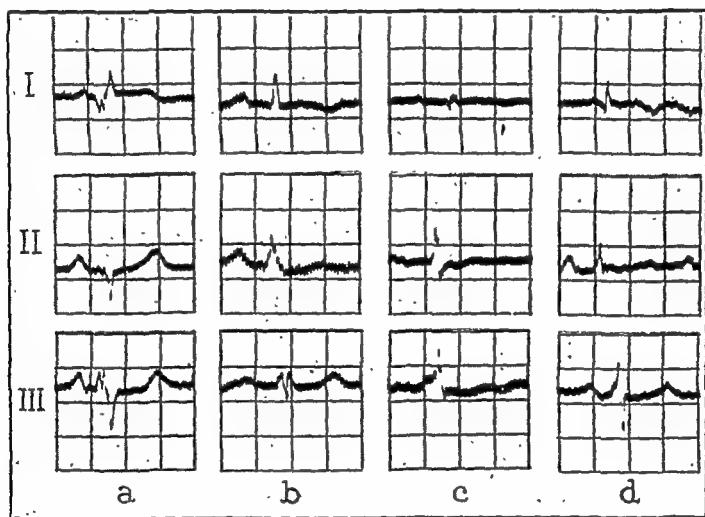


Fig. 1.—Four different patients. *a*, Electrocardiogram taken two days after acute coronary occlusion. Typical Q_1 and T_1 type. Necropsy disclosed acute and chronic infarction of the anterior and apical portion of the left ventricle. *b*, Electrocardiogram taken twenty-four hours after the onset of an attack of acute coronary occlusion. A fairly typical T_1 but no Q pattern is present. Necropsy was not performed. *c*, Electrocardiogram taken twelve weeks after an attack of acute coronary occlusion. The Q_1 type of change is definitely present and strongly supports the diagnosis of myocardial infarction. No R-T pattern can be recognized, probably because of the extreme low amplitude of all deflections in Lead I. *d*, Electrocardiogram taken two years after a typical attack of acute coronary occlusion. Necropsy disclosed ancient and recent infarction in the apex of the left ventricle. No history of recent acute occlusion was obtained. The T_1 pattern is probably present, but it is difficult to be sure of the characteristics of the R-T segment in Lead I. The presence of a fairly well developed Q_1 pattern greatly strengthened the diagnosis of myocardial infarction.

cardial infarction. They classified these changes under the headings of Q_1 and Q_3 types. They found the Q_1 type to be characterized by "the presence of a conspicuous and, in most instances, rather broad Q-wave in Lead I; the absence of Q in Leads II and III; the small amplitude of the largest of the initial deflections in Lead I, and the presence of a conspicuous S in Leads II and III." The Q_3 type is characterized by "the absence of Q in Lead I, the presence of a conspicuous Q in Leads II and III and the relatively small amplitude of the initial ventricular deflections in Lead II."

Since the publication of the article of Wilson and his associates, I have reviewed the 84 electrocardiograms taken of patients who have suffered from attacks of acute myocardial infarction. The diagnosis was based on good clinical evidence or proved at necropsy. It is apparent at once that the combined consideration of the Q and T types of electrocardiographic changes yields more information regarding infarction than does the consideration of either alone.

When a diagnosis of myocardial infarction was based only on clinical evidence, the Q and T patterns were equally characteristic in 18 cases; the Q_1 pattern more characteristic than the T_1 pattern in 6; the T_1 was more typical than the Q_1 type in 10; the Q_3 was more suggestive of acute infarction than the T_3 type in 6; the T_3 was more diagnostic than the Q_3 in 15; the Q_1 pattern of infarction was present in the absence

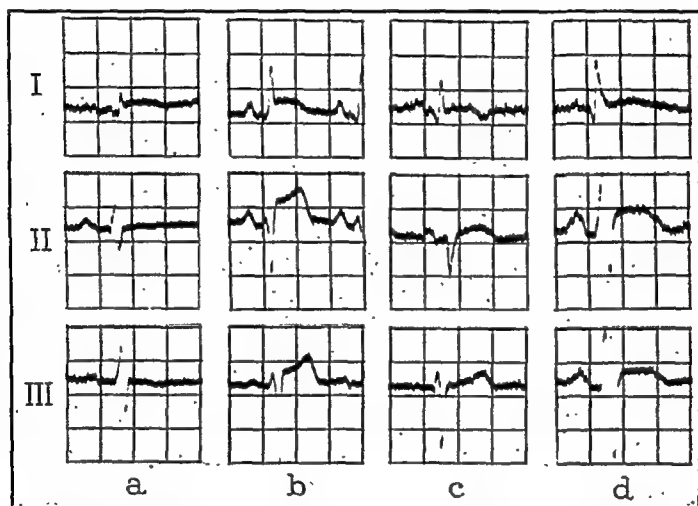


Fig. 2.—Three different patients. *a*, Electrocardiogram taken four months after acute coronary occlusion. Except for the high take-off of the R-T segment in Lead I, there is nothing in the RS-T segments to indicate previous myocardial infarction. The Q_1 pattern is typical, and confirms the diagnosis of infarction. The patient died four months later, but necropsy was not performed. *b*, Electrocardiogram taken two days after acute coronary occlusion. The elevation of the RS-T segments in all leads prevents the recognition of a definite T type of change. The Q_1 pattern is typical of acute myocardial infarction. This patient's infarction was complicated by acute pericarditis. *c*, Electrocardiogram of the same patient as the one represented in *b*, ten days later. Now a typical T_1 and Q_1 type of electrocardiogram is present. *d*, Electrocardiogram taken twenty-four hours after the onset of an attack of acute coronary occlusion complicated by acute pericarditis. The elevated RS-T segment in all leads prevents the classification of the electrocardiogram as a T type. The Q_1 pattern is typical of acute myocardial infarction.

of the T_1 pattern in 1; the T_1 pattern was present alone in 3; the Q_3 pattern occurred alone in none, and in 2 cases, the T_3 pattern was present in the absence of the Q_3 pattern.

When myocardial infarction was proved at necropsy, the Q and T patterns were equally positive in 11 cases; the Q_1 type was more typical than the T_1 type in 3; the T_1 was more characteristic than the Q_1 type in 1; the Q_3 pattern was more suggestive than the T_3 type in 4, and the T_3 pattern offered more evidence of cardiac infarction than the Q_3 pattern in 3.

There are several circumstances that account for the failure of the Q and T types to occur with equal clearness at a given time. In anterior apical infarction, the initial deflection of the electrocardiogram may have a very low amplitude. This so reduces the height of the R-T segment displacement that the change in level and contour of the segment and the inversion of the T-wave are all but unrecognizable. Under these conditions the Q_1 pattern may be present and easily recognizable. Likewise, in infarction in the posterior basal portion of the left ventricle, the amplitude of the initial ventricular deflection in Lead II may be small. On this account, changes in the level and contour of the R-T segment in this lead characteristic of a T_3 type may be difficult to recognize, and the presence of a Q_3 pattern may be of crucial importance. In certain instances infarction in the anterior apical portion of the left ventricle is followed by nothing more than slight rounding and upward displace-

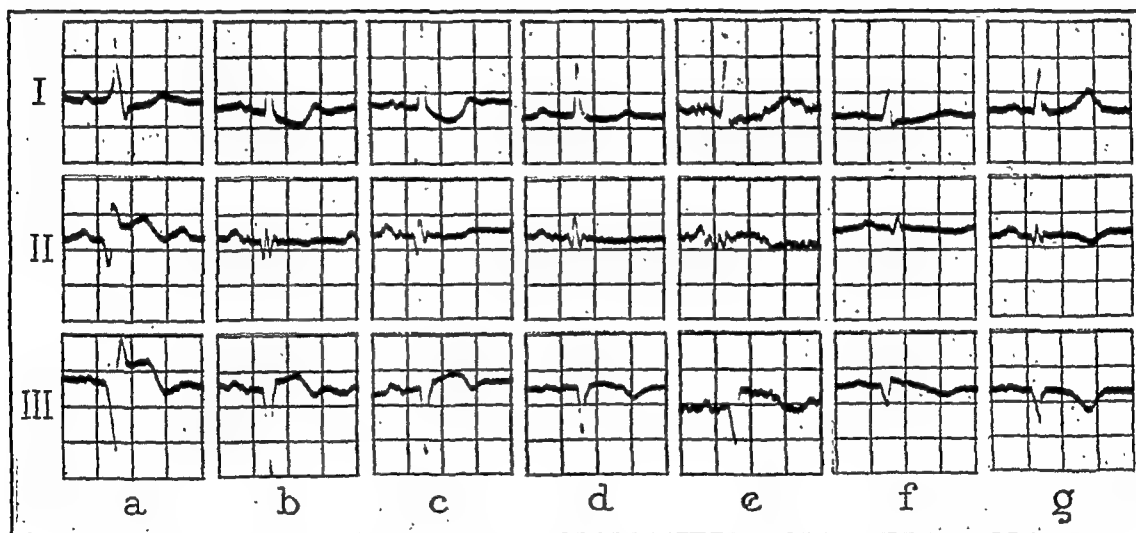


Fig. 3.—Three different patients. *a*, Electrocardiogram taken twenty-four hours after acute coronary occlusion. Typical T_3 and Q_3 patterns are present. Necropsy disclosed an acute infarction in the posterior basal portion of the left ventricle. *b*, Electrocardiogram taken two months after an attack of acute coronary occlusion. A typical Q_3 pattern is present. The RS-T segment changes suggest recent myocardial infarction, but Lead II does not participate in the usual manner. *c*, Tracing of the same patient as the one represented in *b*, one month later. The Q_3 pattern remains typical and diagnostic, but the RS-T in Lead II still does not conform to the usual T_3 type of change. *d*, Tracing taken on the same patient as the one represented in *b* and *c*, six weeks later. The Q_3 pattern remains far more convincing of myocardial infarction than does the T pattern, which now is practically unrecognizable. *e*, Electrocardiogram taken a few days after acute coronary occlusion. There is a typical T_3 type of change, except that the RS-T segment in Lead II is difficult to evaluate. The Q_3 pattern is typical and diagnostic of acute myocardial infarction. *f*, Tracing taken on the same patient as the one represented in *e*, seven days later. The Q_3 pattern is typically developed. The T_3 type still lacks the usual and typical R-T changes in Lead II, possibly owing in part to the low voltage of the deflections in that lead. *g*, Tracing taken on the same patient as the one represented in *e* and *f*, thirteen days later. The T_3 as well as the Q_3 pattern is now typical of recent acute myocardial infarction.

ment of the R-S segment in Lead I, without a corresponding depression of the S-T segment in Lead III. In this instance, the occurrence of a Q_1 pattern greatly strengthens the evidence of infarction.

Either the Q or T patterns may become positive first following acute infarction. They may remain as a relic of infarction equally long.

However, in some instances, the Q pattern may retain its identity longer than the T-pattern, as Wilson pointed out. In tracings under consideration at the clinic, this occurred occasionally, with the T_3 type of electrocardiogram at a stage when the R-T changes in Lead II had returned to normal.

Acute pericarditis complicating acute myocardial infarction frequently produces an anomalous type of electrocardiogram. This complication is prone to be followed by elevation of the RS-T segment in all leads, a picture which cannot be classed definitely as a T_1 or T_3 type of change. This situation may be greatly clarified if a definite Q pattern develops simultaneously.

The Q types of change may be confusing, and actually portions of Q_1 and Q_3 patterns may exist simultaneously in cases in which successive occlusions have occurred. The relic of a Q pattern from a healed acute

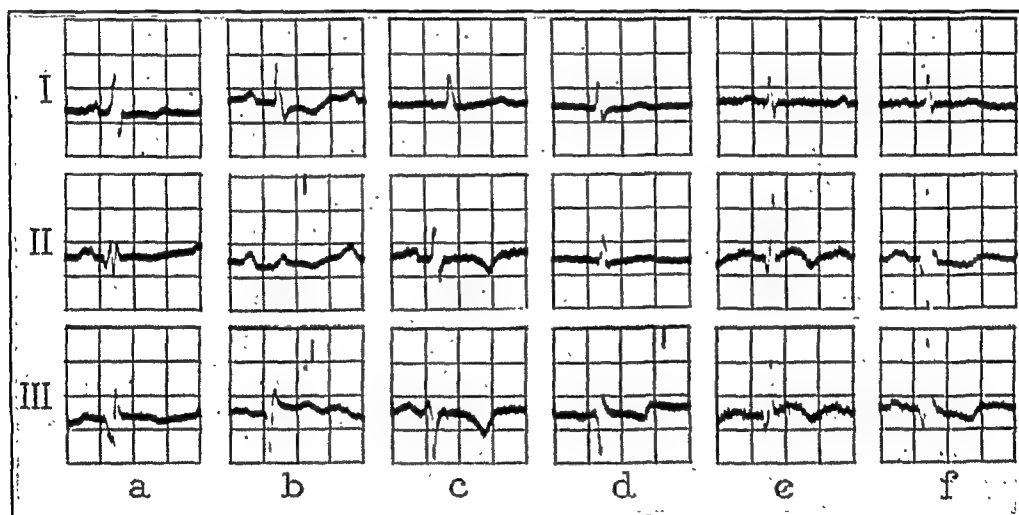


Fig. 4.—Five different patients. *a*, Electrocardiogram taken four months after an attack of acute coronary occlusion. The contour of the R-T segment in Lead III and the slight inversion of the T-wave in Lead II are slightly suggestive of ancient acute cardiac infarction. The presence of a typical Q_3 type of change in the initial deflections tremendously strengthens the diagnosis. *b*, Electrocardiogram taken after acute myocardial infarction. The time of coronary occlusion could not be obtained because the patient was in coma. There is a definite suggestion of a T_3 type of change. There is a typical Q_3 , but no definite Q_2 deflection present. Necropsy disclosed acute infarction of the basal posterior half of the left ventricle. *c*, Electrocardiogram taken two weeks after an attack of acute coronary occlusion. A fairly typical late T_3 pattern of acute myocardial infarction is present, but a Q_3 pattern has not developed. *d*, Electrocardiogram taken two years and eight months after acute coronary occlusion. The electrocardiogram obtained at the time of occlusion showed a typical T_3 type of change. The present electrocardiogram has, as a relic of that event, an R-T segment in Lead III of the T_3 type. However, that change alone does not carry conviction of previous acute cardiac infarction. The Q_3 pattern is typically developed except for the absence of Q_2 . The two patterns taken together constitute strong evidence of previous acute myocardial infarction. *e*, Electrocardiogram taken one week after acute coronary occlusion. The T_3 pattern is typically developed. The Q_3 pattern is atypical in that the initial deflection has its lowest amplitude in Lead I rather than in Lead II. *f*, Tracing taken on the same patient as the one represented in *e*, thirty-nine months later. The Q and T patterns have retained their original characteristics in about equal degree.

infarction may persist in some degree following a second infarction, leading to the development of a Q pattern approximating the opposite type. Here the T type of electrocardiogram may give more nearly unequivocal evidence of acute myocardial infarction than does the Q pattern.

And finally, acute myocardial infarction is followed at times by the development in the electrocardiogram of typical T patterns without the appearance of Q types of changes.

SUMMARY

Acute myocardial infarction is frequently followed by electrocardiographic changes that conform to both the Q and the T patterns indicative of such a condition. In general, the change in the RS-T segment is somewhat more likely to be typically developed and indicative of acute cardiac infarction than is the change in initial ventricular deflection, but occasionally the reverse is true. Not uncommonly neither type of electrocardiographic change is completely typical, but considered together they establish the presence of acute myocardial infarction. Only by such a combined study of the changes in the initial ventricular deflection and of the RS-T segment will one realize the full value of the electrocardiogram as a diagnostic aid.

REFERENCES

1. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.
2. Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14: 195, 1928.
3. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.

CORRELATION OF INITIAL DEFLECTIONS OF VENTRICULAR COMPLEX WITH SITUATION OF ACUTE MYOCARDIAL INFARCTION*

ARLIE R. BARNES, M.D.

ROCHESTER, MINN.

WILSON and his associates described certain changes of the initial deflections of the ventricular complex of the electrocardiogram in association with myocardial infarction. They classified these changes under the headings of Q_1 and Q_3 types. They found the Q_1 type to be characterized by "the presence of a conspicuous and, in most instances, rather broad Q-wave in Lead I; the absence of Q in Leads II and III; the small amplitude of the largest of the initial deflections in Lead I, and the presence of a conspicuous S in Leads II and III." The Q_3 type is characterized by "the absence of Q in Lead I, the presence of a conspicuous Q in Leads II and III, and the relatively small amplitude of the initial ventricular deflections in Lead II." In discussing the relation the Q_1 and Q_3 types of electrocardiograms have to the location of the infarct, they concluded that although infarction in the anterior wall of the left ventricle and the adjacent septum generally was associated with a Q_1 type, yet at times it was associated with the Q_3 type. They described a Q_3 type of electrocardiogram of a patient in whom they found an infarct of the anterior portion of the left ventricle, but in whom later and more detailed examination of the heart disclosed the presence of an old and extensive infarct in the basal portion of the left ventricle. They did not state whether they considered that the latter finding accounted satisfactorily for the discordant electrocardiographic pattern which they reported.

I wish to present the data from 20 cases in which myocardial infarctions occurred and in which electrocardiograms conformed more or less closely to the Q_1 or Q_3 type. These data will appear, for the most part, in legends accompanying the illustrations. Necropsy was performed in all of these cases. In all but 3 cases, there was adequate evidence that acute coronary occlusions had occurred and in one of these 3 cases there was strong presumptive evidence that acute infarction had occurred.

In 7 cases in which electrocardiograms were typical or fairly typical Q_1 types, infarction in each instance was found in the anterior portion of the left ventricle and the adjacent septum. In each of these instances the Q_1 type of electrocardiogram was associated with changes in the tracing conforming more or less closely to the T_1 type.

*From the Division of Medicine, the Mayo Clinic, Rochester, Minn.

In 15 cases in which a Q_3 type of electrocardiogram was obtained, infarction in the posterior basal portion of the left ventricle was found in every instance. In each of these cases the Q_3 and T_3 types of change were present simultaneously.

One of the strongest reasons for believing that a uniform relationship exists between the Q pattern and the situation of infarction is afforded by 2 patients, each of whom suffered two successive acute infarctions; in each of the 2 cases a time interval elapsed and permitted adequate electrocardiographic studies after each infarction. Necropsy was performed on each of these patients. In the first case, acute infarction in the anterior portion of the left ventricle was followed by the development of a $Q_1 T_1$ type of electrocardiogram, and a second acute

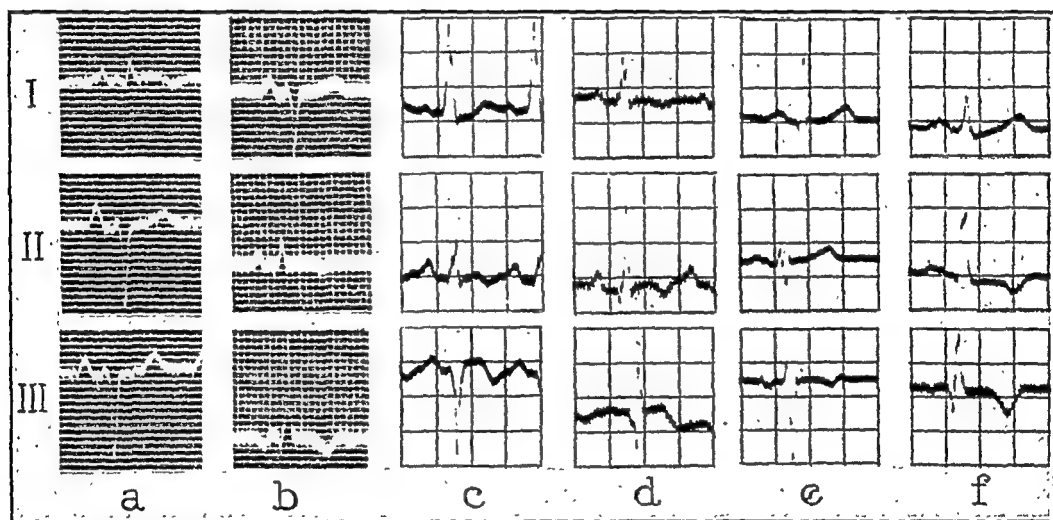


Fig. 1.—Electrocardiograms with shifting deflections. (Case 1) *a*, Q_1 type of electrocardiogram taken seventy-nine days after acute coronary occlusion. Necropsy disclosed ancient large infarction involving the apex, the anterior portion of the left ventricle, and the adjacent interventricular septum. *b*, Electrocardiogram of late T_3 type showing changes in the direction of the Q_3 type; that is, lowest amplitude of the QRS complex in Lead I in tracing *a* is replaced by lowest amplitude in Lead II; prominent S_2 is replaced by small Q_3 , and Q_1 of tracing *a* has disappeared. Tracing *b* was made seven weeks after a second acute coronary occlusion. Necropsy disclosed subacute healing infarction in the posterior basal portion of the left ventricle. (Case 2) *c*, Q_3 type of electrocardiogram taken seventy-nine days after an attack of acute coronary occlusion. *d*, Electrocardiogram taken twenty-four hours after acute coronary occlusion showing a shift toward the Q_1 type. The Q-wave in Lead III is greatly diminished, and the QRS complex now has its smallest amplitude in Lead I. Necropsy was performed six days after the second occlusion and disclosed an old, practically healed infarction in the posterior basal portion, and a recent acute infarction in the anterior and apical portion of the left ventricle. (Case 3) *e*, Electrocardiogram taken one day before acute coronary occlusion. *f*, Electrocardiogram taken three days after acute coronary occlusion with changes tending toward the Q_3 type. Necropsy performed five days later disclosed thrombosis of the right coronary artery with extensive acute infarction in the posterior basal portion of the left ventricle and adjacent interventricular septum. There was an area of acute infarction in the anterior portion of the left ventricle measuring 1.5 cm. in diameter. This latter infarct may account for the fact that the latter tracing does not have a more prominent Q_2 and Q_3 and for the fact that the lowest amplitude of the QRS complex is in Lead I instead of in Lead II.

infarction in the posterior basal portion of the left ventricle caused a complete change of pattern to a late T_3 type and a picture approaching a Q_3 type (Fig. 1 *a* and *b*). That a typical Q_3 type was not reached may possibly be owing to the necessity for completely obliterating the previous Q_1 type. In the second case the order of these changes was

completely reversed; the first posterior basal infarct produced a $Q_3 T_3$ type of change, and the second infarction of the anterior portion of the left ventricle produced RS-T changes, definitely suggestive of a T_1 type of electrocardiogram, and changes in the initial ventricular complex in the direction of a Q_1 type (Fig. 1 *d* and *e*). These changes consist in the decrease in the size of S_3 and the subsequent appearance of the lowest amplitude of the QRS complex in Lead I, whereas previously this complex had its lowest amplitude in Lead II.

In a coordinate study,⁴ I have pointed out that in acute myocardial infarction the T pattern of electrocardiographic changes may be present when the Q pattern is lacking, and vice versa. However, I have not encountered any case with a typical T_1 type of electrocardiogram in which a typical Q_3 pattern occurred, and I have observed no association of typical T_3 and Q_1 patterns. When anterior infarction succeeds posterior infarctions, an atypical Q_3 pattern may remain in association with a T_1 type of electrocardiogram, but the Q_3 pattern is atypical, and

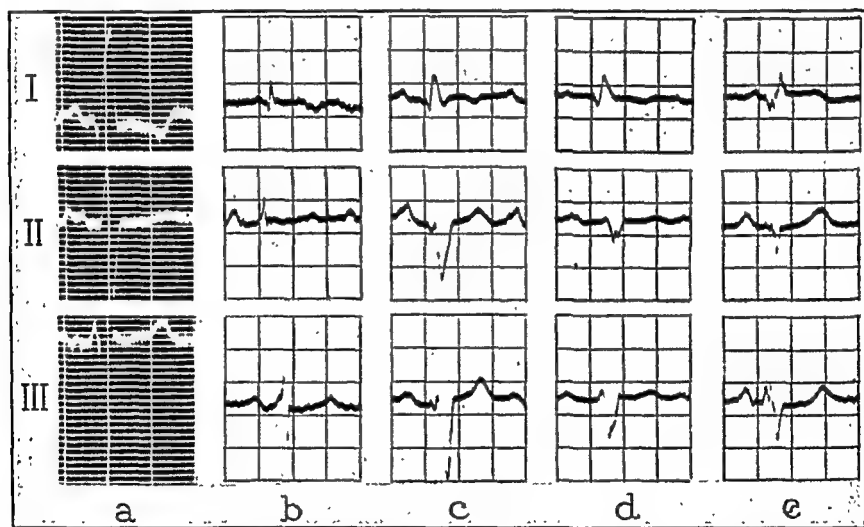


Fig. 2.—Initial deflections of the Q_1 type. (Case 4) *a*, Electrocardiogram conforming to the Q_1 type except that low amplitude of the QRS complex in Lead I is lacking. There was no history of acute coronary occlusion. The patient had hypertensive heart disease. Necropsy performed two months after this tracing was made disclosed high grade coronary sclerosis in all the vessels without occlusion. There were several fibrotic areas in the heart muscle in the region supplied by the anterior descending branch of the left coronary artery. A similar electrocardiogram is frequently obtained in hypertensive heart disease in the absence of coronary sclerosis or myocardial infarction. (Case 5) *b*, This electrocardiogram was obtained two years and three months after an attack of acute coronary occlusion. The patient died within twelve hours after this tracing was made. At necropsy, ancient and recent myocardial infarction was found in the apex and anterior portion of the left ventricle. (Case 6) *c*, This electrocardiogram was obtained fourteen months after an attack of acute coronary occlusion, and eighteen days before the patient's death. There was sclerosis of high degree through the distribution of the coronary artery, but the lumen was not completely occluded. The apex of the left ventricle was the site of a huge healed myocardial infarct. (Case 7) *d*, This electrocardiogram was taken three days before death. Death occurred suddenly, presumably the result of a thrombus which occluded the anterior descending branch at the level of origin of the circumflex branch of the left coronary artery. At necropsy the apex of the heart was thinned out and replaced by fibrous tissue, as was the adjacent interventricular septum. No history of ancient acute occlusion could be obtained. (Case 8) *e*, This electrocardiogram was taken two days after an attack of acute coronary occlusion, and two days before death. At necropsy, the apex and the adjacent anterior portion of the left ventricle and interventricular septum were found to be the site of acute and chronic myocardial infarction. There was aneurysmal dilatation at the apex with marked thinning of the wall of the heart in that region.

a careful study will show that it is veering definitely toward a Q_1 pattern. Wilson has called attention to a number of such published cases, of which the second case in this series, Case 2, is one. Case 1 shows that the same is true when posterior infarction follows anterior infarction, although the residue of the Q_1 pattern is less striking.

Granted that a typical Q_1 T_1 electrocardiographic pattern results from acute infarction in the anterior portion of the left ventricle, it does not follow necessarily that acute infarction in that area will lead to the development of the Q_1 T_1 type. The same may be said of infarction in the posterior basal portion of the left ventricle in respect to the Q_3 T_3 type of electrocardiogram. Extreme low voltage of the initial ventricular deflections, bundle-branch block, multiple acute infarcts involving both the anterior and the posterior portions of the left ventricle, massive widespread infarction, acute pericarditis or the effect of immi-

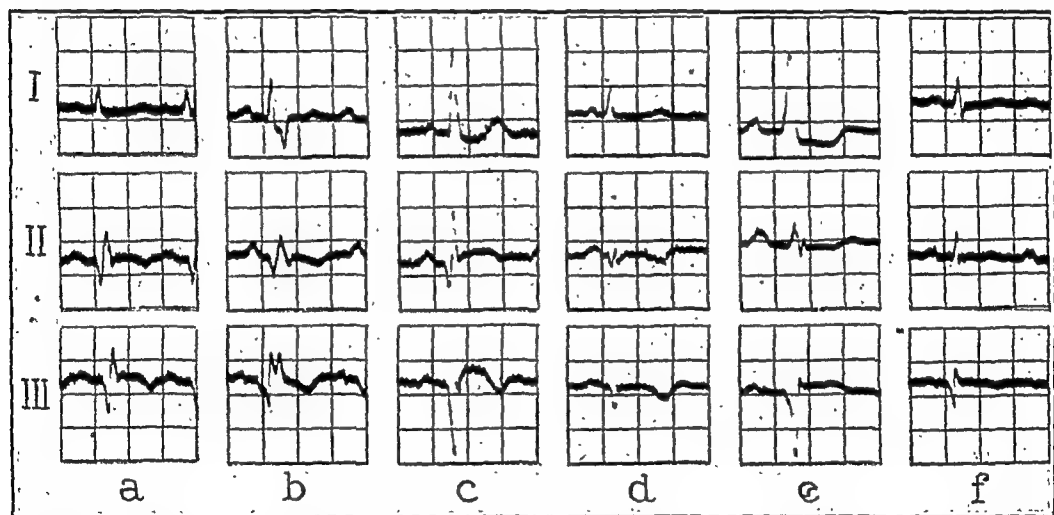


Fig. 3.—Initial deflections of the Q_3 type. (Case 9) a, This electrocardiogram was taken seven days after an attack of acute coronary occlusion and twelve days before death. At necropsy the right coronary artery was found to be occluded by a clot which could be seen projecting from its ostium. Acute myocardial infarction was present in the posterior portion of the left ventricle and extended to the apex. (Case 10) b, This electrocardiogram was taken one day after an attack of acute coronary occlusion and five days before the death of the patient. The QRS complex has a duration of 0.13 second. At necropsy an old infarct in the heart was found to occupy the lower third of the anterior portion of the interventricular septum. This had led to marked thinning and beginning aneurysm of the septum. The right coronary artery was sclerosed markedly and, 6 cm. from its orifice, was completely occluded. There was acute infarction in the posterior basal portion of the left ventricle, the posterior interventricular septum, and in the adjacent region of the right ventricle. This case well illustrates the predominating effect acute infarction exerts over chronic infarction in determining the type of Q T changes that result. (Case 11) c, This tracing was made four days after an attack of acute coronary occlusion and two days before the patient's death. At necropsy the descending branch of the right coronary artery was found to be occluded. There was acute myocardial infarction in the posterior portion of the left ventricle, the posterior interventricular septum, and in the adjacent portion of the right ventricle. (Case 12) d, This tracing was made twenty-four days before death. No history of acute coronary occlusion could be obtained. At necropsy there was extensive acute and subacute infarction in the posterior portion of the left ventricle extending from the apex almost to the base. The right coronary artery was sclerosed, grade 4, but no thrombus in the vessel could be demonstrated. (Case 13) e, This tracing was taken two months before death. No history of acute coronary occlusion could be obtained. At necropsy a large, fibrous scar was found, occupying the posterior basal portion of the left ventricle and extending in an attenuated projection around the interventricular septum toward its anterior third. (Case 14) f, This tracing was made one month before death. No history of acute coronary occlusion could be obtained. At necropsy the circumflex branch was found to be occluded by a thrombus. There was a soft area of infarction in the posterior portion of the left ventricle measuring 5 cm. by 6 cm.

nent death on a tracing may modify, obscure, or prevent the recognition of either the T or the Q patterns. Moreover, the electrocardiographic picture of acute myocardial infarction may be lost if electrocardiograms are not taken in sufficient number, or in proper time relation to acute coronary occlusion.

As Wilson and his associates pointed out, the pathological data and experimental evidence to date do not seem sufficient to attribute the development of the Q_1 type of electrocardiogram to block in the anterior subdivisions of the left branch of the bundle of His, nor to ascribe the Q_3 type to block in the posterior subdivisions of the bundle of His (Figs. 1, 2, 3, and 4).

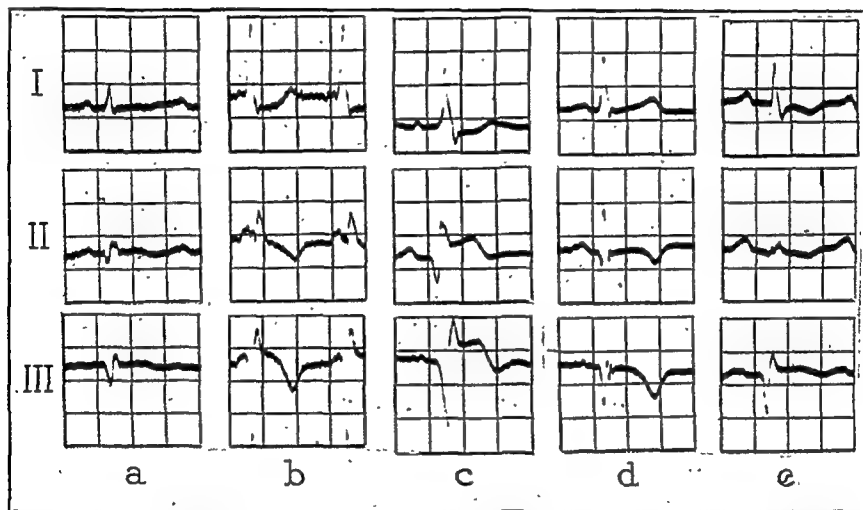


Fig. 4.—Initial deflections of the Q_3 type. (Case 15) *a*, This electrocardiogram was taken nineteen days after an attack of acute coronary occlusion and one day before the patient's death. At necropsy the circumflex branch of the left coronary artery was found to be occluded by a thrombus. The right coronary artery at a point 2 cm. distal to its orifice was nearly occluded. The posterolateral aspect of the left ventricle was the site of acute myocardial infarction. (Case 16) *b*, This tracing was made three days after an attack of acute coronary occlusion and two days before the patient's death. At necropsy an acute myocardial infarct was found to occupy the posterior portion of the left ventricle; it was 2 cm. in width and extended from the base to within 3 cm. of the apex of the left ventricle. (Case 17) *c*, This tracing was made one day following an attack of acute coronary occlusion and three days before the patient's death. At necropsy the left coronary artery was found to be almost occluded just below the point of origin of the circumflex. There was an old healed infarct situated in the anterior apical portion of the left ventricle. There was acute infarction in the posterior basal portion of the left ventricle extending down to and around the apex. The right coronary artery supplied all of the area of acute infarction, but no thrombus in the vessel was described in the original description of the dissection of the vessel. (Case 18) *d*, This tracing was taken one month following an attack of acute coronary occlusion and three years and ten months before the patient's death. Death occurred from acute coronary occlusion, but no tracing was obtained after the fatal attack. At necropsy an area of fibrosis was found in the posterior basal portion of the left ventricle without thinning of the wall. There was a large but scattered distribution of fibrous tissue in the endocardial half of the anterior portion of the left ventricle. (Case 19) *e*, The patient was in coma on admission and no history of coronary occlusion could be obtained. This tracing was taken two days before the patient's death. At necropsy a large area of acute infarction in the posterior half of the left ventricle was found. This area is supplied by the circumflex branch of the left coronary artery; the branch was occluded.

The electrocardiogram of Case 20 was too dim for photographic reproduction. It was of the Q_3 type, and at necropsy an area of healed infarction in the posterior wall of the left ventricle in the region supplied by the right coronary artery was found.

CONCLUSIONS

1. The modifications of the initial ventricular deflections are correlated with the site of myocardial infarction.

2. Electrocardiograms typical of, or closely approximating, the typical Q_1 type are found to be associated with acute or healing acute infarction in the anterior and apical portion of the left ventricle and the adjacent interventricular septum.

3. The Q_3 type of electrocardiogram is found to be associated with acute or healing acute infarction in the posterior basal portion of the left ventricle and in the adjacent interventricular septum.

4. Not all acute infarctions in the left ventricle are followed by the characteristic Q patterns.

REFERENCES

1. Barnes, A. R.: Q and T Types of Electrocardiograms: Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Occlusion, *AM. HEART J.* 9: 722, 1934.
2. Idem: Electrocardiographic Localization of Myocardial Infarcts, *M. Clin. N. America* 14: 671, 1930.
3. Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14: 195, 1933.
4. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.

ELECTROCARDIOGRAPHIC PATTERN OBSERVED FOLLOWING ACUTE CORONARY OCCLUSION COMPLICATED BY PERICARDITIS

REPORT OF CASES*

ARLIE R. BARNES, M.D.
ROCHESTER, MINN.

THE electrocardiogram taken following acute coronary occlusion has been of more assistance in the diagnosis of this disease than in that of any other cardiac lesion. Changes of the RS-T segment in the electrocardiogram occur that not only indicate the presence of acute myocardial infarction,⁸ but also, under proper conditions,^{1, 5} permit its localization in the heart before death. Changes in the initial deflection of the electrocardiogram have been described lately that, when typically developed, likewise indicate the occurrence of acute myocardial infarction¹⁰ and have a definite localizing value.²

In attempting to evaluate electrocardiographic changes in cases in which acute coronary occlusion is suspected, the changes in the RS-T segment indicative of that condition may not be developed typically. As has been pointed out elsewhere, a combined study of the Q and RS-T patterns frequently will yield more information than a study of either pattern alone.³

The most characteristic feature of the RS-T segment changes following acute coronary occlusion is that an elevation of the R-T segment in Lead I is accompanied by a depression of the S-T segment in Lead III and vice versa. However, in some instances of infarction involving the anterior apical portion of the left ventricle, the only change that occurs in the RS-T segment in the first few days is elevation of the R-T segment in Lead I without a corresponding depression of the S-T segment in Lead III. This change, if the patient survives sufficiently long, usually is followed later by the development of a typical T₁ type of electrocardiogram. Another variation of the change in the RS-T segment following acute infarction consists in elevation or dome-shaped upward rounding of the RS-T segments in all leads. Obviously this change does not permit its classification as a T₁ or T₃ type, and yet the changing electrocardiogram is strong evidence of the acute coronary obstruction. Moreover, in its later stages, this electrocardiographic pattern is at times followed by inversion of the T-waves in all leads, which further complicates the attempt to classify the change as a T₁ or T₃ type. Evidence is submitted here to indicate that such an electrocardiogram is the result of acute coronary occlusion complicated by acute pericarditis.

*From the Division of Medicine, The Mayo Clinic, Rochester, Minn.

CASE 1.—A man, aged sixty years, was admitted to the hospital May 1, 1926. He was having a typical attack of coronary occlusion at the time of his admission. A definite pericardial friction rub was present on the second day. An electrocardiogram, taken seven days after his admission, showed an elevated take-off of the RS-T segment in each lead, the segments tending to have a definite dome shape (Fig. 1 *a*). A tracing taken two weeks later showed a definite inversion of the T-wave in Lead I of a Pardee type, and T_2 was now upright, peaked and exaggerated, a typical late T_1 type of electrocardiogram (Fig. 1 *b*). The patient recovered from this attack but died of pneumonia sixteen months later. At necropsy the anterior descending branch of the left coronary artery was found to be occluded in its lower third. Healed pericarditis completely obliterated the pericardial sac. The lower third of the anterior portion of the left ventricle and the adjacent portion of the interventricular septum were the site of an old infarction. There was marked thinning of the anterior and apical portions of the left ventricle with an organized thrombus beneath this area.

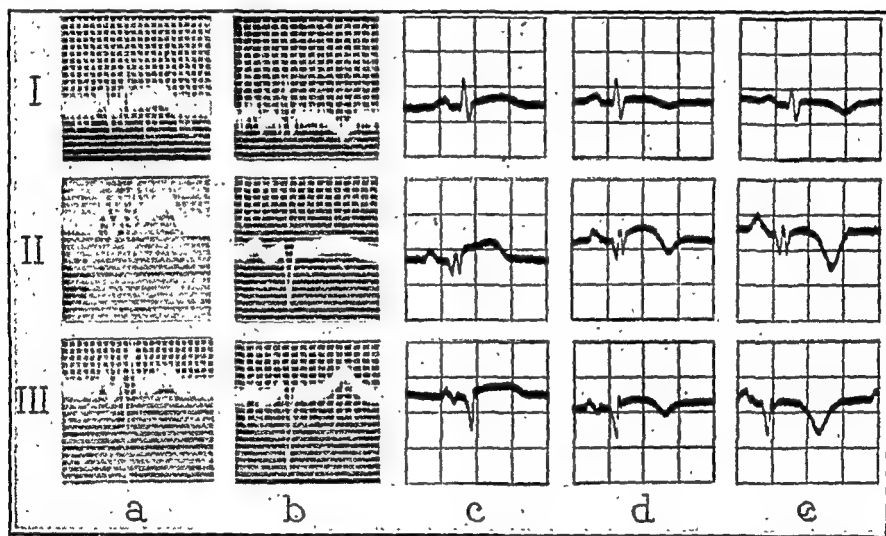


Fig. 1.—(Case 1) Standard electrocardiogram taken *a* seven days; and *b* twenty-one days after acute coronary occlusion; (Case 2) standard electrocardiogram taken *c* seven days, *d* eleven days, and *e* twenty-six days after acute coronary occlusion.

CASE 2.—A man, aged seventy-two years, was admitted June 21, 1929. Twenty-four hours previously he had been seized by an attack of acute epigastric pain which was still present on admission. On the day following, a definite pericardial friction rub was heard, and a diagnosis of acute coronary occlusion was made. The electrocardiogram taken on the seventh day showed an elevation and upward rounding of the RS-T segments in all leads without inversion of the T-waves (Fig. 1 *c*); a tracing taken four days later was similar except that the T-waves were inverted in all leads (Fig. 1 *d*). A third tracing, taken nineteen days after the first, showed a return of the S-T segments to the isoelectric level, with inversion of the T-waves in all leads (Fig. 1 *e*). At no stage could the electrocardiogram be classified as a T_1 or a T_2 type. The patient recovered from this attack and was allowed to go home. He was having marked symptoms of prostatic obstruction, and suprapubic cystostomy was performed October 30, 1929, which he withstood without incident. He died December 2, 1929, following suprapubic prostatectomy. At necropsy the pericardium was found to be adherent except over the posterior surface of the heart. The lower two-thirds of the anterior portion of the left ventricle were composed largely of scar tissue and were thin; the wall measured 0.8 cm. in thickness. The left coronary artery was sclerosed, graded 4.

That every patient in whom pericarditis complicates acute coronary occlusion does not have an electrocardiogram in which RS-T segments show elevation and upward rounding in all leads is shown by the following case.

CASE 3.—A man, aged sixty-seven years, had acute substernal pain and was admitted to the hospital as an emergency case. The electrocardiogram taken twenty-four hours after the onset of the pain showed slight elevation of R-T₁ with shallow inversion of the T-wave in that lead. The S-T segment in Lead II was slightly depressed (Fig. 2 *b*). Four days later a definite pericardial friction rub was present, and a tracing taken at that time did not show any additional changes (Fig. 2 *c*). The S-T segment in the fourth lead* in each of these tracings was distinctly elevated. The patient died on the seventh day of rupture of the heart at the site of acute infarction, with hemorrhage into the pericardium. At necropsy the anterior descending branch of the left coronary artery was found to be occluded

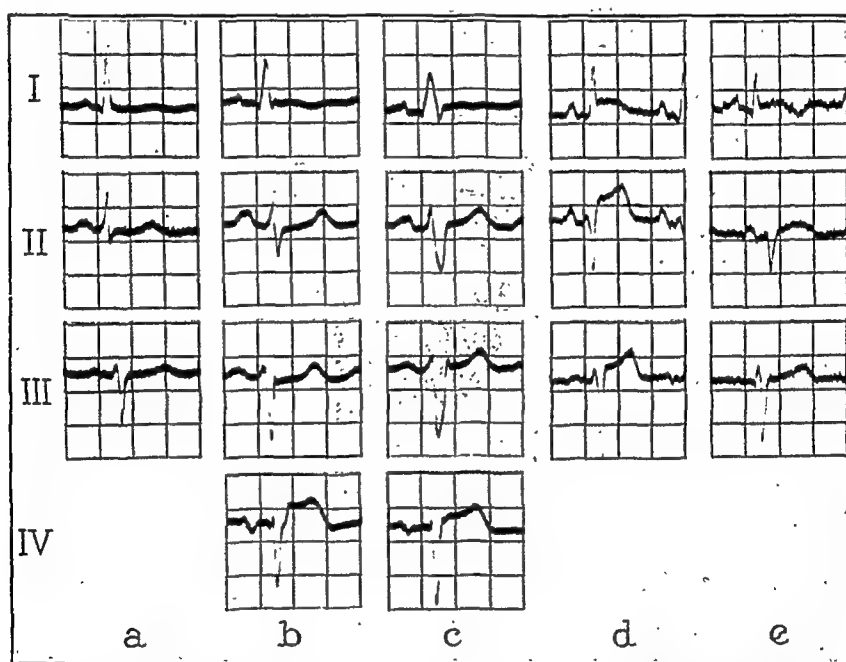


Fig. 2.—(Case 3) Standard electrocardiogram and the fourth lead taken *a* two and a half years before, *b* twenty-four hours after, and *c* five days after the onset of acute coronary occlusion; (Case 4) standard electrocardiogram taken *d* three days, and *e* thirteen days after the onset of acute coronary occlusion.

by a thrombus. A region over the apex of the heart and extending up into the anterior portion of the left ventricle, and measuring 8 cm. by 5 cm., was the site of acute infarction. This area was overlaid by a thick fibrinous blood-stained exudate. There was a recent fibrinous exudate over the base of the heart, extending well onto the great vessels.

In the fourth case the Q pattern indicated the site of infarction at a time when it could not be predicted from the character of the RS-T segments where the infarction would be found.

*In taking the fourth lead I have placed the left arm electrode on the anterior part of the thorax and the right arm electrode on the posterior part of the thorax. In tracings taken in this way the T-wave is normal when upright and abnormal when inverted. This application of the electrodes is opposite to that described and employed by Wolferth and Wood.

CASE 4.—A woman, aged sixty-nine years, suffering from chronic occlusive arterial disease of the legs, had an attack of acute coronary occlusion while under observation. A definite pericardial friction rub was heard three days after the onset of the attack. The electrocardiogram taken at that time showed elevation of the RS-T segments in all leads without inversion of the T-wave (Fig. 2 *d*). This electrocardiogram is a typical Q_i type and is indicative of anterior apical infarction.² Daily electrocardiograms for the next five days showed no essential changes. The electrocardiogram taken thirteen days after the onset of acute coronary occlusion revealed RS-T changes that were now late typical manifestations of a T_i type (Fig. 2 *e*) and indicated the anterior apical portion of the left ventricle as the site of infarction, as did the Q_i pattern from the beginning. The patient made a satisfactory recovery and was dismissed from the hospital about one month after her attack.

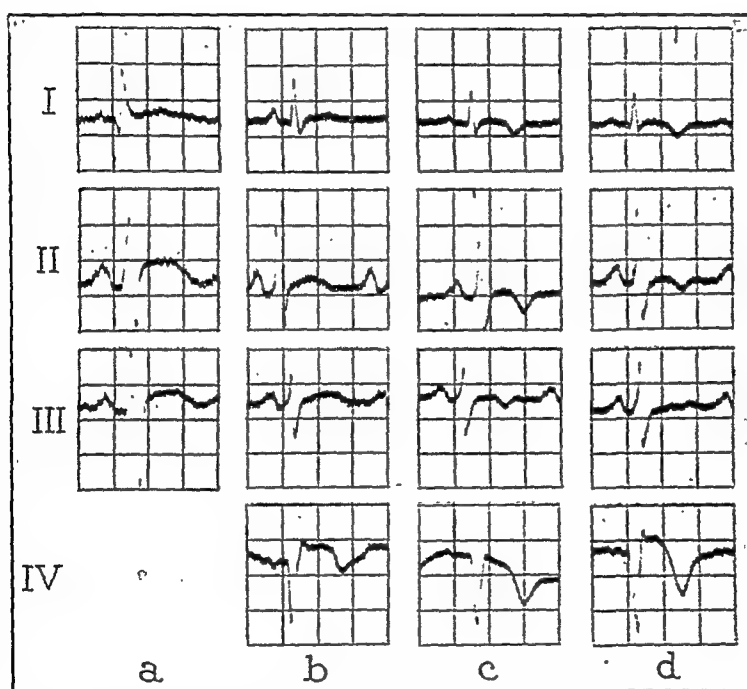


Fig. 3.—(Case 5) Standard electrocardiogram taken *a* the second day after acute coronary occlusion; (Case 6) standard electrocardiogram and the fourth lead taken *b* eight days after, *c* fourteen days after, and *d* thirty-five days after the onset of acute coronary occlusion.

CASE 5.—A man, aged fifty-seven years, suffered an acute attack of coronary occlusion, and a pericardial friction rub was audible on the day of the occlusion. Electrocardiograms were taken two and six days after this occlusion, and the tracings were practically identical. There was elevation or dome-shaped rounding of the RS-T segments in all leads. The Q_i pattern was definitely present, indicative of anterior apical infarction² (Fig. 3 *a*). No further tracings were obtained. The patient's convalescence was uneventful, and he was dismissed from the hospital twenty-four days after the onset of occlusion.

CASE 6.—A man, aged sixty-one years, had an attack of acute coronary occlusion October 25, 1933, and was admitted to the hospital two days later. A pericardial friction rub was plainly audible on the second day. An electrocardiogram taken four days later showed upward rounding, but no elevation of the RS-T segments in all leads (Fig. 3 *b*). The S-T segment in the fourth lead was elevated and the T-wave was inverted. A tracing taken six days later showed definite inversions

of T-waves in all leads (Fig. 3 *c*). The electrocardiogram taken twenty-seven days after the first tracing showed a decrease of negativity of T_s, and the R-T segment in Leads I and II had become much more characteristic of a late T₁ type (Fig. 3 *d*). A typical Q₁ pattern now was present that indicated that the myocardial infarction had involved the anterior and apical portion of the left ventricle.² The patient's convalescence was uneventful, and he was dismissed from the hospital after thirty-four days of observation and treatment. The elevation of the S-T segment in the fourth lead was striking. Whether or not this is a feature confined to cases of acute myocardial infarction complicated by pericarditis, will require further study.

CASE 7.—A man, aged fifty-nine years, was admitted to the hospital in a typical attack of coronary occlusion. Two days later a definite pericardial friction rub was audible. An electrocardiogram obtained that day showed elevation of the RS-T segment in all leads (Fig. 4 *b*). A tracing taken twenty-one days after the second tracing showed inversion of all the T-waves and a Q₁ type of electrocardiogram

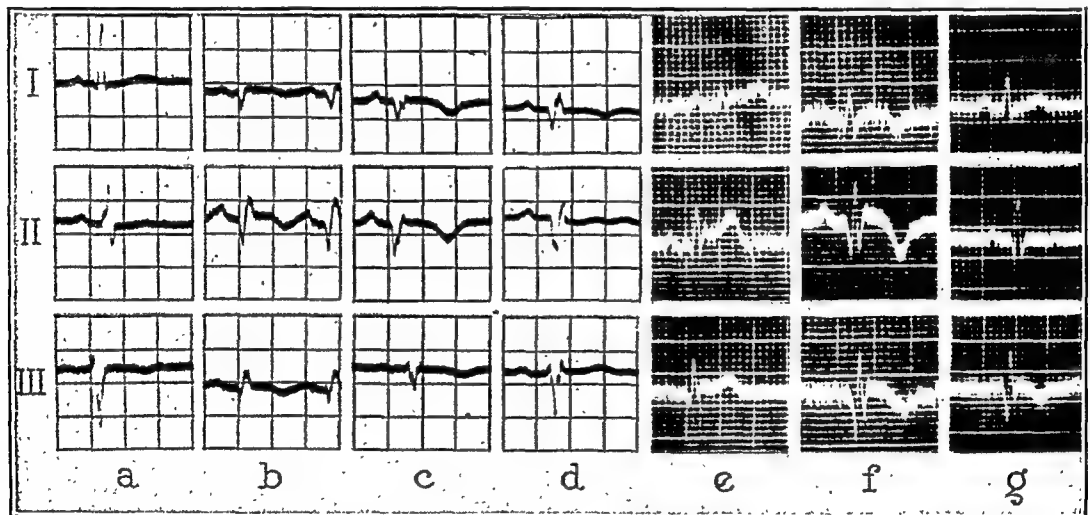


Fig. 4.—(Case 7) Standard electrocardiogram taken *a* three days before, *b* the day of, *c* twenty-one days after and *d* two years after acute coronary occlusion; (Case 8) standard electrocardiogram taken *e* forty-eight hours after, *f* eight days after, and *g* six months and eight days after the onset of acute coronary occlusion.

indicative of infarction of the anterior apical portion of the left ventricle (Fig. 4 *c*). In an electrocardiogram taken two years later, the T-wave in Lead III was upright, and the R-T segment in Lead I was a fairly typical late relic of a T₁ type of change (Fig. 4 *d*).

CASE 8.—A man, aged forty-eight years, was admitted during a severe attack of coronary occlusion, the pain lasting ninety-six hours. No friction rub was ever heard in this case. A tracing taken on the day of admission showed an elevated take-off of the RS-T segment in all leads (Fig. 4 *e*) with T-waves somewhat high in all leads but especially in Lead II. This tracing may be compared with that of a dog (Fig. 1 *d*) in the article by Mann and me following the reaction of the pericardium to operative injury. This type of tracing persisted for four days, and on the sixth day after admission the T-waves were negative in all leads (Fig. 4 *f*). Except for the fact that the initial deflection had its smallest amplitude in Lead I, this tracing could be classified as a Q₃ type indicative of infarction of the posterior basal portion of the left ventricle. A tracing taken six months

after the latter tracing showed the T-wave in Lead I upright, and it showed R-T segments in Leads II and III that were typical relics of ancient infarction in the posterior basal portion of the left ventricle (Fig. 4 *g*). In this case pericarditis was not observed clinically, yet these tracings resembled those previously shown when pericarditis was known to be a factor, and they suggested that that complication was present. No way exists of excluding from consideration infarction of both the posterior and the anterior portion of the left ventricle, in the original prolonged attack.

COMMENT

That pericarditis, complicating acute coronary occlusion in man, may modify the RS-T segments of the electrocardiogram in the foregoing manner receives support from other experimental and clinical data. Scott, Feil and Katz⁹ recorded elevation of the RS-T segment in all leads in electrocardiograms of patients in whom sudden hydropericardium had developed. They reasoned that this electrocardiographic change resulted from hydrostatic pressure exerted on the heart and that it led to compression of the vascular channels and produced anoxemia, reduced cardiac output, and impaired coronary flow. They⁷ were able to produce similar changes in the electrocardiograms of dogs by rapid distention of the pericardial sac with fluids. Barnes and Mann found that profound changes in the RS-T segment of the electrocardiogram occurred when the dog's pericardium was opened without molesting the coronary circulation. Subsequent necropsy of these animals indicated that extensive pericarditis followed this procedure. They believed that the modifications of the RS-T segment that followed resulted from the pericarditis. Fowler, Rathe and Smith observed similar changes in the electrocardiogram following production of pericarditis, and they demonstrated by microscopic study that the superficial layers of the myocardium were involved in the inflammatory process. They concluded it was this injury to the superficial layers of the myocardium that was responsible for the modifications in the electrocardiogram. There is no reason to suspect in the clinical cases presented here that pericardial effusion of any degree, or sudden in its accumulation, occurred. I am inclined to believe that the injury which the superficial layers of the myocardium sustain in the pericardial reaction accounts for the peculiar electrocardiographic change, an interpretation supported by the experiments just cited.

The types of electrocardiograms presented here have been difficult of interpretation heretofore. They could not be classed clearly as either of T₁ or T₂ type. Lacking this classification, they could not be utilized to predict the situation of the infarct. They were so bizarre that they sometimes led to the doubt as to whether there were electrocardiographic patterns of RS-T changes typical of acute cardiac infarction, inasmuch as they were encountered in the electrocardiograms of patients who were undoubtedly victims of acute coronary occlusion. True enough, the

changing character of the electrocardiogram indicated the presence of infarction, but the absence of the usual pattern was disturbing, none the less. I believe this study reveals the significance of this type of electrocardiogram, and the picture of elevation of the RS-T segment in all leads that occurs in a case of occlusion should lead to careful attempts to elicit a pericardial friction rub. Inasmuch as the friction rub may be heard only temporarily, the occurrence of this type of tracing strongly suggests the presence of pericarditis, even though evidence of its presence may otherwise escape the ear of the examiner.

It is further interesting to note that, except in Cases 1 and 8, there was some feature of the electrocardiograms that suggested that its character was dependent on infarction of the anterior and apical portions of the left ventricle. Whether infarction of the posterior basal portion of the left ventricle complicated by pericarditis can produce this picture, remains to be established by correlation of such electrocardiographic changes with cardiac pathology.

It is noteworthy that in some of these electrocardiograms, even though the RS-T pattern in its early form is distorted so as not to permit localization, the Q pattern is fully developed, and it indicates not only the presence but also the site of acute myocardial infarction.

CONCLUSIONS

The electrocardiograms of patients in whom acute coronary occlusion is complicated by pericarditis differ from the type of RS-T changes associated with uncomplicated, acute coronary occlusion. The typical feature of the electrocardiogram, seen in coronary occlusion associated with pericarditis in its early stages, consists of elevation or upward rounding of the RS-T segment in all leads. This may be followed by inversion of the T-wave in all leads. In some instances, it is followed by the development of a T pattern that can be classified definitely as a late relic of acute coronary occlusion. In the stage when the RS-T segment is elevated in all leads, the Q pattern may be typically developed, not only indicating infarction, but also pointing to the situation of the infarct in the left ventricle.

REFERENCES

1. Barnes, A. R.: Electrocardiographic Localization of Myocardial Infarcts, *M. Clin. N. America* 14: 671, 1930.
2. Idem: Correlation of Initial Deflections of Ventricular Complex With Situation of Acute Myocardial Infarction, *AM. HEART J.* 9: 728, 1934.
3. Idem: Q and T Types of Electrocardiograms: Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, *AM. HEART J.* 9: 722, 1934.
4. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
5. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.

6. Fowler, W. M., Rathe, H. W., and Smith, F. M.: The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *AM. HEART J.* 8: 370, 1933.
7. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion. II. Experimental, *AM. HEART J.* 5: 77, 1929.
8. Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14: 195, 1928.
9. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion. I. Clinical, *AM. HEART J.* 5: 68, 1929.
10. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
11. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.

THE VELOCITY OF PULMONARY AND PERIPHERAL VENOUS BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN CARDIOVASCULAR DISEASE

THEIR RELATION TO CLINICAL TYPES OF CIRCULATORY FAILURE*

GEORGE P. ROBB, M.D., AND SOMA WEISS, M.D.
BOSTON, MASS.

THE velocity of blood flow in pathological states of the circulation is already well known. Investigations of recent years¹⁻⁶ have revealed a characteristic slowing of the blood flow in cardiovascular disease with circulatory failure, in myxedema and in polycythemia vera; and an acceleration of the circulation in thyrotoxicosis and anemia. In compensated heart disease, as well as in arterial hypertension and emphysema, the velocity of blood flow has been found to be normal or but slightly retarded.

Although concordant results have been obtained with the various methods employed, the radium emanation method² is particularly valuable in that it provides a separate estimation of the velocity of blood flow through the lungs and through the peripheral vascular areas. Such a differential index of the functional state of the greater and lesser circulations is of practical as well as theoretical value in the diagnosis and treatment of disorders of the circulation.

The cyanide method was devised in order to provide a simple, objective method for the separate measurement of the velocity of the pulmonary and of the peripheral venous blood flow in man. This method and the observations made in normal subjects were reported in a previous communication,⁷ in which evidence was presented to show that sodium cyanide could safely be administered to man within a wide range of dosage, and that the cyanide "circulation time" was a reliable measure of the velocity of blood flow.

In order to ascertain whether the cyanide method would furnish a reliable measure of the velocity of blood flow in heart failure, measurements of the pulmonary circulation time, of the peripheral venous circulation time, and of other quantitative indices of the state of the pulmonary and the systemic circulations, as well as clinical observations, were made in patients with compensated heart disease and in patients with various degrees of circulatory failure. The pulmonary and venous circulation times obtained were then compared with those obtained with the

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

radium emanation method in a group of subjects with similar clinical states. For a more precise evaluation, the cyanide and the dye or glucose circulation times were determined in the same person.

METHODS USED

The arterial pressure was determined with the aid of a mercury manometer; the venous pressure, by the direct venipuncture method of Moritz and von Tabora⁸ with the arm resting at the level of the right auricle. In determinations of the vital capacity of the lungs, a calibrated spirometer was used. Measurements of the crude pulmonary circulation time and of the peripheral venous circulation time were made with the cyanide method in the usual manner⁷; in orthopneic, as in normal subjects, the antecubital injections were made with the arm resting at the level of the right auricle. Determinations of the dye (or glucose) arm-to-femoral circulation time were made with the vital red method of Hamilton and his associates,⁹ in which the procedure is as follows: The subject reclines on his right side; the injection of dye is made into the antecubital vein of the elevated left arm; and the blood samples for colorimetric analysis are obtained by puncture of the femoral artery.

RESULTS

Measurements of the pulmonary and the peripheral venous circulation times, of the venous pressure and of the vital capacity were made in fifty-six patients with hypertensive, arteriosclerotic, syphilitic, or rheumatic heart disease. Of this group, forty-six were totally incapacitated and presented the symptoms and signs of circulatory failure while at rest; the remainder were ambulatory and without evidence of decompensation. The clinical observations and circulatory measurements are presented in Tables I to V, inclusive.

Patients With Cardiovascular Disease Without Circulatory Failure

No clinical evidence of circulatory failure could be detected in the ten patients with compensated heart disease (Table I), although in two instances (Cases 2 and 10) there was a history of circulatory failure. The vital capacity averaged 1,572 c.c. per square meter (980 to 2,100 c.c. per square meter), which is 34 per cent less than the average normal value of 2,376 c.c. per square meter²; the pulmonary circulation time, 13 seconds (10 to 15 seconds), or 23 per cent longer than the average normal (10.6 seconds)⁷; and the arm venous circulation time, 5.3 seconds (3 to 12 seconds), or 18 per cent longer than the average normal (4.5 seconds). The venous pressure was essentially normal, 7.7 cm. of water (5 to 10 cm.).

Except for the proportionately greater reduction in the vital capacity, these measurements lie within the normal range, although there is a tendency toward stasis and retardation of blood flow.

TABLE I

THE PULMONARY AND PERIPHERAL VENOUS CIRCULATION TIMES IN PATIENTS WITH CARDIOVASCULAR DISEASE WITHOUT CIRCULATORY FAILURE

CASE NO.	AGE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRES-SURE	VITAL CAPACITY		CYANIDE CIRCULATION TIME			DIAGNOSIS
			SYS-TOLIC	DIAS-TOLIC		OB-SERVED	PER SQUARE METER	ARM TO CAROTID	CRUDE PUL-MONARY	VENOUS	
	yrs.	per min.	mm. Hg	mm. Hg	cm. H ₂ O	c.c.	c.c.	sec.	sec.	sec.	
1	59	96	165	110	+ 8	1600	980	13	10	3	Arterial hypertension; myocardial degeneration; emphysema.
2	23	78	150	35	-	3300	1800	16	11	5	Rheumatic heart disease; mitral stenosis and insufficiency; aortic stenosis and insufficiency.
3	56	84	125	80	-	2300	1190	20	12	8	Myocardial degeneration; emphysema.
4	35	92	100	65	+ 8	2850	1740	16	13	3	Rheumatic heart disease; mitral stenosis and insufficiency.
5	35	80	215	130	+ 8	3200	2100	25	13	12	Malignant hypertension.
6	57	78	140	80	+ 7	1800	1100	16	14	2	Myocardial degeneration; emphysema; arteriosclerosis.
7	49	60	120	75	+ 5	3250	1830	18	14	4	Myocardial degeneration; arteriosclerosis.
8	68	84	130	75	-	2200	1270	18	15	3	Myocardial degeneration; emphysema; arteriosclerosis.
9	66	58	170	75	-	3200	1840	22	15	7	Arterial hypertension; myocardial degeneration.
10	44	82	185	120	+10	3200	1870	19	-	-	Arterial hypertension; myocardial degeneration.
Average	49	79	150	84	+ 7.7	2690	1572	18.3	13	5.2	

Patients With Cardiovascular Disease With Circulatory Failure

Hypertensive Heart Disease.—Circulatory failure was present in seventeen patients with arterial hypertension and hypertensive heart disease (Table II). The majority of these patients suffered from paroxysmal cardiac dyspnea. They all exhibited orthopnea and other clinical signs of pulmonary stasis¹⁰; whereas only approximately one-half of them showed peripheral edema. None showed cardiac arrhythmia.

These patients with circulatory failure are divided into two groups: Group A, showing failure of the pulmonary circulation only; and Group B, showing failure of the entire circulation. In the nine patients of Group A, the vital capacity ranged between 550 and 1,640 c.c. per square meter, with an average of 1,049 c.c., which is 56 per cent below normal. The pulmonary circulation time varied between 13 and 22 seconds, averaging 16.8 seconds, or 58 per cent longer than the normal time. The arm venous circulation time, on the other hand, varied between 2 and 8 seconds, with an average of 4.1 seconds, which is 9 per cent *shorter* than the normal time. The venous pressure was essentially normal, averaging 8.2 cm. of water (6 to 11 cm.).

Subsequent observations made in Cases 3, 5, 6 and 7 (Table II) after slight to moderate clinical improvement had occurred, revealed an increase in average vital capacity from 968 to 1,440 c.c. per square meter; a decrease in the pulmonary circulation time from 17 to 15.5 seconds, and in the venous circulation time from 4.2 to 3 seconds; and a lowering of the venous pressure from 9.5 to 6.8 cm. of water. In the four subjects (Cases 2, 7, 8, 9) who subsequently showed more advanced circulatory failure, on the other hand, there was a decrease in the average vital capacity from 1,238 to 1,093 c.c. per square meter; an increase in the pulmonary circulation time from 17.5 to 22.5 seconds, and in the venous circulation time from 3.5 to 4.5 seconds; and an elevation of the venous pressure from 7.5 to 11.8 cm. of water. Thus, coincident with clinical improvement there was a tendency toward a return to normal in these aspects of the circulation; whereas with more advanced failure, a further deviation from normal occurred.

In the eight patients of Group B who exhibited failure of both pulmonary and peripheral circulations the vital capacity averaged 1,055 c.c. per square meter (700 to 1,310 c.c.), or 56 per cent less than normal. Both the pulmonary and the peripheral circulation times were increased, the pulmonary circulation time to an average of 22.5 seconds (13 to 35 seconds), or 112 per cent longer than the normal time, and the arm venous circulation time to 8.8 seconds (2 to 25 seconds), or 96 per cent longer. The venous pressure, averaging 16.3 cm. of water (11 to 23 cm.), was 123 per cent greater than the average normal pressure.²

Four subjects of Group B (Cases 12, 15, 16, 17) subsequently showed moderate clinical improvement, with the disappearance of peripheral

TABLE II

THE PULMONARY AND PERIPHERAL VENOUS CIRCULATION TIMES IN PATIENTS WITH HYPERTENSIVE HEART DISEASE WITH CIRCULATORY FAILURE

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				MM. HG	MM. HG		OBSERVED	PER SQUARE METER		ARM TO CAROTID	CRUDE PULMONARY	VENOUS	
	YEARS		PER MIN.	MM. HG	MM. HG	CM. H ₂ O	C.C.	C.C.	SEC.	SEC.	SEC.	SEC.	
<i>Group A. Patients with failure of the pulmonary circulation and normal peripheral circulation</i>													
1	49	4/20/31	108	210	120	8	1500	970	15*	15	13	2	Marked failure. Intense dyspnea. Orthopnea 40°. Edema 0. Died 4 days later.
2	25	6/29/31	100	175	125	6	1800	1260	-	17	13	4	Malignant hypertension. Mild circulatory failure. Orthopnea 20°. Edema 0.
		8/18/31	104	235	160	14	950	680	-	21	18	3	Condition worse. Orthopnea 40°. Edema 14°. Died 2 months later.
3	52	4/29/32	96	210	115	10	1750	1110	15	16	14	2	Uremia. Intense dyspnea at rest. Orthopnea 25°. Edema 0.
		5/13/32	84	195	95	7	2140	1350	16	17	14	3	Slight improvement. Dyspnea on slight exertion. Orthopnea 0°. Edema 0.
4	56	1/12/31	94	170	110	6	-	-	-	22	15	7	Moderate failure. No dyspnea at rest. Orthopnea 45°. Edema 0.
5	60	9/23/31	92	160	85	9	1000	550	19	24	16	8	Moderate failure. Orthopnea 40°. Edema 0.
		11/ 5/31	72	160	85	4	2150	1180	-	19	14	5	Moderate improvement. Orthopnea 15°. Edema 0. Died 6 weeks later.

*Glucose circulation time.

TABLE II—CONT'D

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
							OBSERVED	PER SQUARE METER					
				MM. HG	MM. HG					ARM TO CAROTID	CRUDE PULMONARY	VENOUS	
YEARS			PER MIN.			CM. H ₂ O	C.C.	C.C.	SEC.	SEC.	SEC.	SEC.	
6	62	4/24/31	76	220	110	8	2600	1360	15*	21	19	2	Mild failure. Dyspnea on slight exertion. No orthopnea nor edema.
		5/ 7/31	62	210	95	8	3500	1830	-	20	19	1	Improved. Dyspnea on moderate exertion.
7	71	11/19/31	64	220	100	11	1500	850	23	24	19	5	Moderate failure. Orthopnea 30°. Edema 0.
		11/30/31	72	220	90	8	2500	1400	-	18	15	3	Improved. Orthopnea 15°. Edema 0. No dyspnea.
		1/ 8/32	80	210	105	7	2250	1280	24	21	19	2	Condition worse. Orthopnea 25°. Edema 0. Died 5 weeks later.
8	57	4/ 8/31	72	155	95	6	2700	1640	24*	24	20	4	Frequent attacks of paroxysmal dyspnea. Orthopnea 45°. Edema 0.
		5/29/31	72	155	105	10	2600	1580	-	40	33	7	Condition worse. Continuous dyspnea. Frequent attacks of paroxysmal dyspnea. Edema 1+. Died 2 weeks later.
9	56	4/20/31	100	220	145	10	1300	650	24*	25	22	3	Uremia. Intense dyspnea. Orthopnea 30°. Edema 0.
		5/ 8/31	82	250	145	16	1700	850	-	26	20	6	Condition worse. Orthopnea 0°. Edema 1+.
Group B. Patients with failure of both pulmonary and peripheral circulations													
10	42	6/15/32	114	212	156	15	2630	-	-	15	13	2	Congestive failure. Intense dyspnea. Orthopnea 70°. Edema 3+.
11	63	3/28/31	70	180	105	11	2750	1310	-	25	17	8	Arteriosclerosis. Moderate decompensation. Orthopnea 30°. Edema 1+.
*Glucose circulation time.													

*Glucose circulation time.

TABLE II—CONT'D

CASE NO.	AGE YEARS	DATE	HEART RATE PER MIN.	ARTERIAL PRESSURE		VENOUS PRESSURE CM. H ₂ O	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				MM. HG	DIASTOLIC		OBSERVED	PER SQUARE METER		ARM TO FEMORAL	ARM TO CAROTID	CRUDE PULMONARY	
				MM. HG			C.C.	C.C.	SEC.	SEC.	SEC.	SEC.	
12	50	5/28/31	90	165	95	12	1200	700	-	23	19	4	Mild asthmatic seizure. Orthopnea 40°. Edema 2+.
		6/18/31	80	150	80	8	-	-	21	24	20	4	Moderate improvement. No orthopnea nor edema.
13	60	10/29/31	84	240	130	17	-	-	-	26	20	6	Uremia. Marked Cheyne-Stokes' respiration. Orthopnea 20°. Edema 4+. Died.
14	57	10/ 2/31	68	160	100	17	1300	740	36	40	24	16	Advanced failure. Orthopnea 60°. Edema 3+.
15	54	9/25/31	104	195	150	23	2200	1250	24	30	26	4	Uremia. Orthopnea 15°. Edema 1+.
		10/ 1/31	84	195	125	14	2350	1330	18	22	17	5	Moderate improvement. Died 2 weeks later.
16	46	10/ 8/31	84	180	95	17	2550	1260	28	31	26	5	Severe failure. Orthopnea 45°. Edema 2+.
		11/ 7/31	84	160	115	7	3320	1700	25	25	18	7	Cheyne-Stokes' respiration.
		11/ 5/31	84	170	110	9	3250	1650	28	30	23	7	Improved. Orthopnea 15°. Edema 0.
													Slightly worse. Orthopnea 20°. Edema 0. Died 8 months later.
17	68	3/14/31	72	170	115	18	1800	1070	-	60	35	25	Severe failure. Orthopnea 60°. Anasarca. Cheyne-Stokes' respiration.
		4/15/31	60	150	95	7	3000	1770	35*	35	27	8	Moderate improvement. Slight orthopnea. Edema 0.

*Glucose circulation time.

edema and either improvement or disappearance of orthopnea. The average vital capacity was increased from 1,070 to 1,600 c.c. per square meter; the pulmonary circulation time was shortened from 26.5 to 20.5 seconds; and the venous pressure was lowered from 17.5 to 9.5 cm. of water. In the one instance with retarded venous circulation, the circulation time decreased from 25 to 8 seconds. Following a transient period of improvement Case 16 became more severely decompensated; coincidentally the pulmonary circulation time was prolonged from 18 to 23 seconds, but the vital capacity and other aspects of the circulation showed no change.

Arteriosclerotic Heart Disease.—The observations made in eleven patients with generalized arteriosclerosis, myocardial degeneration and circulatory failure are presented in Table III. There was no evidence of antecedent arterial hypertension in any of these patients. In two cases the blood pressure was temporarily elevated during congestive failure, but it returned to normal with clinical improvement. All the members of this group exhibited orthopnea and cyanosis, and they all suffered from chronic pulmonary emphysema as well as from myocardial disease.

Six patients (Group A) showed clinical evidence of failure of the pulmonary circulation without peripheral circulatory abnormality. The average vital capacity was 968 c.c. per square meter (710 to 1,170 c.c.), or 59 per cent below normal; the pulmonary circulation time, 22.3 seconds (15 to 33 seconds), or 110 per cent longer than the normal time; the venous circulation time, 6.7 seconds (3 to 14 seconds), or 49 per cent longer than the normal time; and the venous pressure, 6.7 cm. of water (3 to 11 cm.), or essentially normal. Coincident with clinical improvement in three cases (Cases 2, 4, 5), there was a considerable increase in the vital capacity (1,000 to 1,533 c.c. per square meter), and a decrease in the pulmonary circulation time (22.3 to 17.7 seconds), but no significant change in the previously normal venous circulation time (5.3 to 5 seconds) or in the venous pressure (7.7 to 5.7 cm. of water).

In five patients (Group B) in whom there was failure of both the pulmonary and the peripheral venous circulations, the vital capacity varied between 680 and 1,310 c.c. per square meter, with an average value of 975 c.c., or a reduction of 59 per cent; the pulmonary circulation time ranged from 22 to 45 seconds, with an average of 28 seconds, or a prolongation of 162 per cent; the venous circulation time measured from 2 to 20 seconds, with an average of 9.8 seconds, or a prolongation of 112 per cent; and the venous pressure varied between 7 and 20 cm. of water, with an average of 14.6 cm., or an increase of 100 per cent. Clinical improvement occurred in all of these patients, and coincidentally there was an increase in the vital capacity from 975 to 1,315 c.c. per square meter; a decrease in the pulmonary circulation time from 28 to 19.2 seconds, and in the venous circulation time from 9.8 to 6.2 seconds; and a decrease in the venous pressure from 14.6 to 5.4 cm. of water.

TABLE III

THE PULMONARY AND PERIPHERAL VENOUS CIRCULATION TIMES IN PATIENTS WITH ARTERIOSCLEROTIC HEART DISEASE WITH CIRCULATORY FAILURE

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VE-NOUS PRES-SURE		VITAL CAPACITY		DYE CIRCULA-TION TIME	CYANIDE CIRCULATION TIME			REMARKS
				SYS-TOLIC	DIAS-TOLIC	SYS-TOLIC	DIAS-TOLIC	OB-SERVED	PER SQUARE METER	ARM TO FEMORAL	ARM TO CAROT-ID	CRUDE PULMO-NARY	VE-NOUS	
	YRS.		PER MIN.	MM. HG	MM. HG	MM. HG	MM. HG	C.C.	C.C.	SEC.	SEC.	SEC.	SEC.	
<i>Group A. Patients with failure of the pulmonary circulation and normal peripheral circulation</i>														
1	57	6/6/31	96	125	95	3	1400	720	16	20	15	5	5	Marked emphysema. Intense dyspnea. Orthopnea 40°. Edema 0. Died 3 months later.
2	58	5/ 8/31	90	145	85	8	1500	710	18	21	18	3	3	Mild attack of paroxysmal dyspnea. Auricular fibrillation. Orthopnea 45°. Edema 0.
3	73	6/23/31	92	100	70	6	2850	1360	17	17	15	2	2	Moderate improvement. Orthopnea 20°. Edema 0.
4	68	4/29/31 10/ 9/31 10/30/31	96 84 68	125 140 135	78 90 75	11 5 6	-- 2100 3500	-- 1170 1940	-- 30 21	24 28 24	19 21 18	5 7 6	5	Moderate failure. Orthopnea 30°. Edema 0. Moderate failure. Orthopnea 35°. Edema 0. Marked improvement. Ambulatory. Orthopnea 0°. Edema 0.
5	71	3/14/31	64	110	55	10	1900	1120	--	34	28	6	6	Emphysema. Mild failure. Orthopnea 15°. Edema 0.
6	63	3/27/31 6/ 6/31	64 108	110 125	50 95	5 3	2200 2300	1300 1120	-- --	27 47	20 33	7 14	7	Moderate improvement. Orthopnea 10°. Mild failure. Healed cardiac infarct. Auricular fibrillation. Orthopnea 35°. Edema 0.

TABLE III—CONT'D

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VE-NOUS PRES-SURE	VITAL CAPACITY		DYE CIRCULA-TION TIME	CYANIDE CIRCULATION			REMARKS
				SYS-TOLIC	DIAS-TOLIC		OB-SERVED	PER SQUARE METER		ARM TO CAROT-ID	CRUDE PULMO-NARY	VE-NOUS	
	YRS.		PER MIN.	MM. HG	MM. HG	CM. H ₂ O	C.C.	C.C.	SEC.	SEC.	SEC.	SEC.	
Group B. Patients with failure of both pulmonary and peripheral circulations													
7	63	12/ 7/32	104	170	105	17	1400	700	26	24	22	2	Severe failure. Cheyne-Stokes' respiration. Orthopnea 60°. Edema 3+.
		12/31/32	84	155	95	2	2300	1150	22	22	19	3	Slight improvement. Orthopnea 20°. Edema 1+.
8	46	3/17/32	146	100	90	17	2520	1310	27	27	24	3	Died 5 months later. Intense dyspnea. Orthopnea 50°. Edema 0. Auricular fibrillation.
		3/24/32	82	110	80	6	3800	1990	22	23	19	4	Moderate improvement. Auricular fibrillation. Orthopnea 20°. Died suddenly 3 weeks later.
9	80	1/14/32	80	150	100	12	1190	680	37	33	24	9	Advanced failure. Auricular fibrillation. Intense dyspnea. Orthopnea 30°. Edema 4+.
		1/16/32	72	125	65	7	1240	710	31	30	19	11	Slight improvement. Orthopnea 20°. Edema 3+.
10	64	4/ 3/31	80	140	90	7	-	-	-	40	25	15	Died suddenly 2 days later. Severe failure. Cheyne-Stokes' respiration. Auricular fibrillation. Orthopnea 80°. Edema 1+.
		4/22/31	68	110	75	5	2000	1150	28*	26	21	5	Moderate improvement. Mild periodic breathing. Orthopnea 20°. Edema 0.
11	70	2/11/32	144	100	80	20	2000	1210	-	65	45	20	Severe failure. Auricular fibrillation. Cheyne-Stokes' respiration. Orthopnea 25°. Edema 4+.
		2/19/32	70	120	75	7	2350	1410	20	26	18	8	Marked improvement. Chest clear. No orthopnea nor edema.

*Glucose circulation time.

TABLE IV
THE PULMONARY AND PERIPHERAL VENOUS CIRCULATION TIMES IN SYPHILITIC HEART DISEASE WITH CIRCULATORY FAILURE

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				SYSTOLIC	DIASTOLIC		OBSERVED	PER SQUARE METER		ARM TO CAROTID	CRUDE PULMONARY	VENOUS	
	YEARS		PER MIN.	MM. HG	MM. HG	CM. H ₂ O	C.O.	C.O.	SEC.	SEC.	SEC.	SEC.	
Group A. Patients with failure of the pulmonary circulation and normal peripheral circulation													
1	33	6/2/32	104	160	45	8	800	450	15	17	14	3	Aortic regurgitation. Intense dyspnea. Orthopnea 80°. Edema 0. Died 5 days later.
2	56	11/14/32	100	210	50	8	2500	1470	-	24	20	4	Aortic regurgitation. Moderate failure. Orthopnea 30°. Edema 0.
3	41	10/30/31	100	125	50	9	1300	875	-	31	23	8	Aortic regurgitation. Coronary disease. Advanced failure. Orthopnea 40°. Edema 0. Died 8 months later.
4	54	3/16/31	76	185	50	11	1800	1010	-	35	27	8	Aortic regurgitation. Aneurysm. Dyspnea on slight exertion. No orthopnea nor edema.

TABLE IV—CONT'D

CASE NO.	AGE	DATE	HEART RATE	PRESSURE ARTERIAL		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				MM. HG	MM. HG		OBSERVED	PER SQUARE METER		ARM TO CAROTID	CRUDE PULMONARY	VENOUS	
YEARS	PER MIN.				CM. H ₂ O		C.C.	C.G.	SEC.	SEC.	SEC.	SEC.	
<i>Group B. Patients with failure of both pulmonary and peripheral circulations</i>													
5	43	3/6/32	72	105	65	19	2500	1440	23	35	22	13	Aortic regurgitation. Aneurysm. Moderate failure. Orthopnea 40°. Edema 1+.
6	61	5/9/31	104	110	65	6	1600	1065	-	31	24	7	Aortitis. Coronary occlusion. Moderate failure. Slight dyspnea. Orthopnea 10°. Edema 1+.
7	52	6/7/32	92	158	55	19	2330	1455	30	34	26	8	Died suddenly 12 hours later. Aortic regurgitation. Aneurysm. Advanced failure. Slight dyspnea. Orthopnea 25°. Edema 3+.
8	49	6/18/32	96	175	40	13	2400	1500	34	37	27	10	No change. Died 6 weeks later.
		11/11/31	168	120	95	27	-	-	-	42	36	6	Aortic aneurysm. Auricular fibrillation. Intense dyspnea. Orthopnea 90°. Edema 0.
		11/11/31	104	110	95	25	-	-	-	42	-	-	Two hours later moderate improvement. Orthopnea 60°. Edema 0. Died 2 days later.
9	46	6/13/32	108	104	74	12	1650	1000	-	54	43	11	Aortitis with coronary disease. Paroxysmal dyspnea. Advanced failure. Moderate dyspnea. Orthopnea 30°. Edema 3+.
		10/21/32	108	108	76	-	-	-	68	65	-	-	Condition worse. Intense dyspnea. Cheyne-Stokes' respiration. Orthopnea 45°. Edema 2+. Died 24 hours later.

Syphilitic Heart Disease.—The nine patients with syphilitic heart disease suffered from paroxysmal cardiac dyspnea and showed the signs and symptoms of circulatory failure. As indicated in Table IV, aortic insufficiency was present in six of these patients, aortic aneurysm in four, and both of these lesions in three. In two patients (Cases 6 and 9) who exhibited no clinical or roentgen-ray evidence of aneurysm or aortic valve disease, syphilitic aortitis with almost complete occlusion of the coronary ostia was found at necropsy.

Four patients (Group A), although decompensated, presented no clinical evidence of peripheral circulatory failure. The vital capacity ranged from 450 to 1,470 c.c. per square meter, with an average of 950 c.c., which is 60 per cent less than normal; the pulmonary circulation time varied between 14 and 27 seconds, with an average of 21 seconds, or 98 per cent greater than normal; while the average arm venous circulation time of 5.8 seconds (3 to 8 seconds) and the venous pressure of 9 cm. of water (8 to 11 cm.) showed relatively slight increases of 29 and 23 per cent, respectively.

The five patients of Group B were more severely decompensated and showed generalized circulatory failure. The average vital capacity, which was 1,240 c.c. per square meter (1,000 to 1,455 c.c.), was 48 per cent lower than normal; the pulmonary circulation time, 30.2 seconds (22 to 43 seconds), 185 per cent longer than the normal time; the venous circulation time, 9 seconds (6 to 13 seconds), 100 per cent longer than the normal time; and the venous pressure, 16.6 cm. of water (6 to 27 cm.), 127 per cent above the average normal pressure. In Case 7, with advanced myocardial insufficiency, the absence of clinical improvement following rest, digitalization and dehydration corresponded with the absence of significant circulatory change.

Rheumatic Heart Disease.—The nine patients (Table V) who suffered from rheumatic valvular heart disease with circulatory failure exhibited the clinical and roentgenological signs of mitral disease. Aortic valvular disease coexisted in one instance (Case 3), functional tricuspid insufficiency in two instances (Cases 3 and 4), and cardiac arrhythmia in three. In the two patients (Cases 5 and 7) who suffered from recurrent paroxysmal cardiac dyspnea and pain, severe coronary arterial disease complicated the rheumatic heart disease. Case 1 (Group A), although decompensated, showed no peripheral failure. The venous pressure of 6 cm. of water and the venous circulation time of 5 seconds are essentially normal, and are in striking contrast to the vital capacity of 1,280 c.c. per square meter, which was 46 per cent below normal, and to the pulmonary circulation time of 19 seconds, which was 79 per cent above normal.

In the eight cases (Group B) with failure of both pulmonary and peripheral circulations, the vital capacity, which averaged 1,050 c.c. per square meter (510 to 1,510 c.c.), was 56 per cent less than normal; the

TABLE V
THE PULMONARY AND PERIPHERAL VENOUS CIRCULATION TIMES IN RHEUMATIC HEART DISEASE WITH CIRCULATORY FAILURE

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				SYSTOLIC	DIASTOLIC		OBSERVED	PER SQUARE METER		ARM TO FEMORAL	ARM TO CAROTID	VENOUS	
YEARS			PER MIN.	MM. HG	MM. HG	CM. H ₂ O	C.C.		SEC.	SEC.	SEC.	SEC.	
Group A. Patients with failure of the pulmonary circulation and normal peripheral circulation													
1	42	10/29/31	92	125	75	6	2700	1280	-	24	19	5	Mitral stenosis and regurgitation. Moderate failure. Orthopnea 20°. Edema 0.
Group B. Patients with failure of both pulmonary and peripheral circulations													
2	50	6/15/32	132	128	90	18	1950	1030	-	39	21	18	Mitral stenosis and regurgitation. Auricular flutter. Moderate failure. Orthopnea 30°. Edema 1+.
3	13	9/ 6/31	112	135	60	25	1350	980	-	30	23	7	Mitral and aortic stenosis and regurgitation. Tricuspid regurgitation. Advanced failure. Orthopnea 0°. Edema 4+.
4	14	9/23/31	104	110	45	11	1550	1150	-	18	14	4	Marked improvement. Edema 0.
		9/13/31	104	120	95	20	1800	1230	-	30	24	6	Mitral stenosis and regurgitation. Auricular fibrillation. Tricuspid regurgitation. Advanced failure. Orthopnea 0°. Edema 4+.
5	50	11/10/32	84	115	80	10	2200	1050	26	26	24	2	Mitral stenosis and regurgitation. Coronary disease. Orthopnea 30°. Edema 2+.
		11/30/32	60	110	65	5	4150	1980	24	28	22	6	Improved. Ambulatory. Orthopnea 10°. Edema 0.

TABLE V—CONT'D

CASE NO.	AGE	DATE	HEART RATE	ARTERIAL PRESSURE		VENOUS PRESSURE	VITAL CAPACITY		DYE CIRCULATION TIME	CYANIDE CIRCULATION TIME			REMARKS
				SYS- TOLIC	DIA- STOLIC		OBSERVED	PER SQUARE METER		ARM TO CAROTID	GRUDE PULMONARY	VENOUS	
YEARS			PER MIN.	MM. HG	MM. HG	CM. H ₂ O	C.G.	C.G.	SEC.	SEC.	SEC.	SEC.	
6	53	3/30/31	100	130	80	14	1400	510	-	42	24	18	Mitral stenosis and regurgitation. Auricular fibrillation. Moderate failure. Orthopnea 20°. Edema 2+.
7	57	10/ 5/31	100	110	85	25	1300	830	32	36	30	6	Mitral stenosis and regurgitation. Coronary disease. Advanced failure. Orthopnea 45°. Edema 1+.
8	26	10/13/31 12/ 1/31	88 104	115 125	75 95	6 22	2150 1900	1370 1270	18 -	19 55	17 35	2 20	Improved. Orthopnea 20°. Edema 0. Mitral stenosis and regurgitation. Advanced failure. Orthopnea 35°. Edema 4+. Died 2 months later.
9	30	2/27/32	132	135	80	19	2560	1510	24	25	-	-	Mitral stenosis and regurgitation. Regular rhythm. Advanced failure. Orthopnea 40°. Edema 4+. Died suddenly 24 hours later.

pulmonary circulation time, averaging 25.9 seconds (21 to 35 seconds), and the venous circulation time, averaging 11 seconds (2 to 20 seconds), were both 144 per cent greater than normal; and the venous pressure, averaging 19.1 cm. of water (10 to 25 cm.), was 162 per cent above normal. Coincident with clinical improvement in three patients (Cases 3, 5 and 7) there was an increase in the average vital capacity from 953 to 1,500 c.c. per square meter; a decrease in the pulmonary circulation from 25.7 to 17.7 seconds and in the venous circulation time from 5 to 4 seconds; and a decrease in the venous pressure from 20 to 7.1 cm. of water.

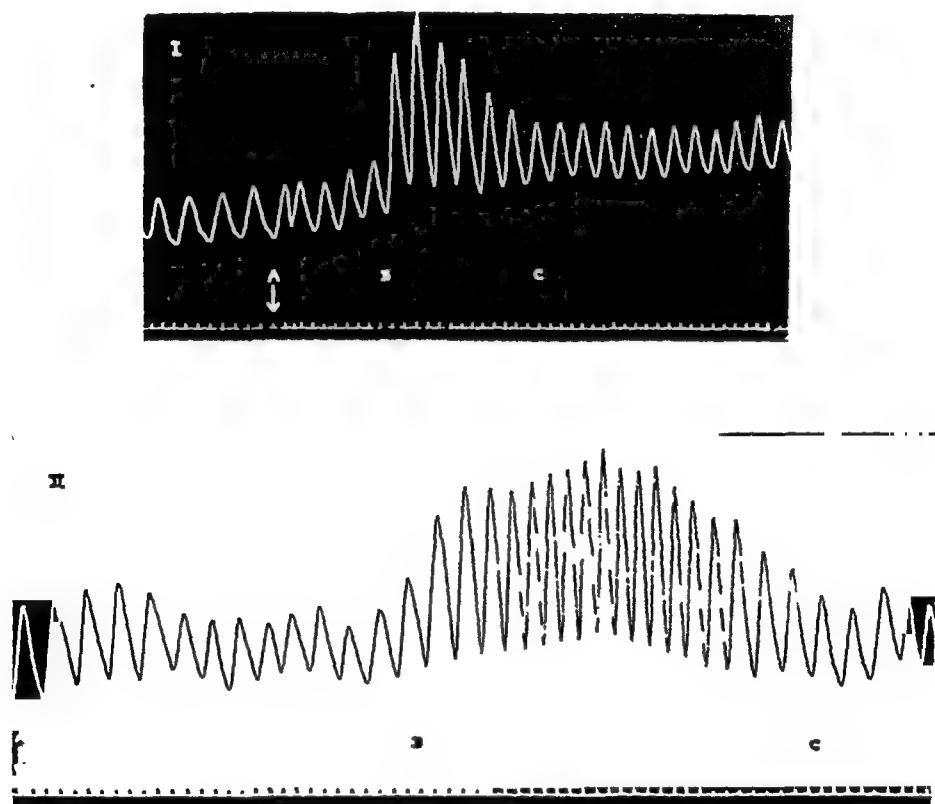


Fig. 1.—Comparison of the respiratory response to cyanide in a normal subject (tracing 1) and in a patient with congestive failure (tracing 2). A, Injection; B, onset of respiratory stimulation (10 and 29 sec., respectively); C, return to normal respiration (24 and 60 sec., respectively). Note the more delayed intense and prolonged stimulation of respiration in the patient with congestive failure.

The Dosage of Cyanide and Respiratory Response in Circulatory Failure

The reaction to cyanide in patients with cardiac decompensation differs in several respects from the reaction in normal subjects. Smaller doses of cyanide as a rule cause adequate respiratory stimulation. The average optimal dose for antecubital injection, 5.2 mg., or 0.26 c.c. of 2 per cent aqueous solution, or 0.084 mg. per kilogram, was approximately 25 per cent smaller than the average normal dose. As in normal subjects, approximately two-thirds of the antecubital dose gave a comparable response from jugular injection. In view of the increase in dosage found necessary with the radium emanation¹¹ and histamine³

methods as a result of "stringing out" in the blood stream, this reduction in dosage is particularly significant and may indicate a lowering of the threshold for cyanide stimulation during circulatory failure. In our experience no untoward results have followed the administration of sodium cyanide to patients with circulatory failure except in one subject with malignant hypertension and nausea, in whom vomiting occurred.

The respiratory response to cyanide in circulatory failure is characterized by a relatively gradual onset, a more moderate increase in the rate and the amplitude of respiration, and a more gradual return to natural breathing. In severe failure, the response may extend over a period several times as long as that occupied by the transient type of reaction

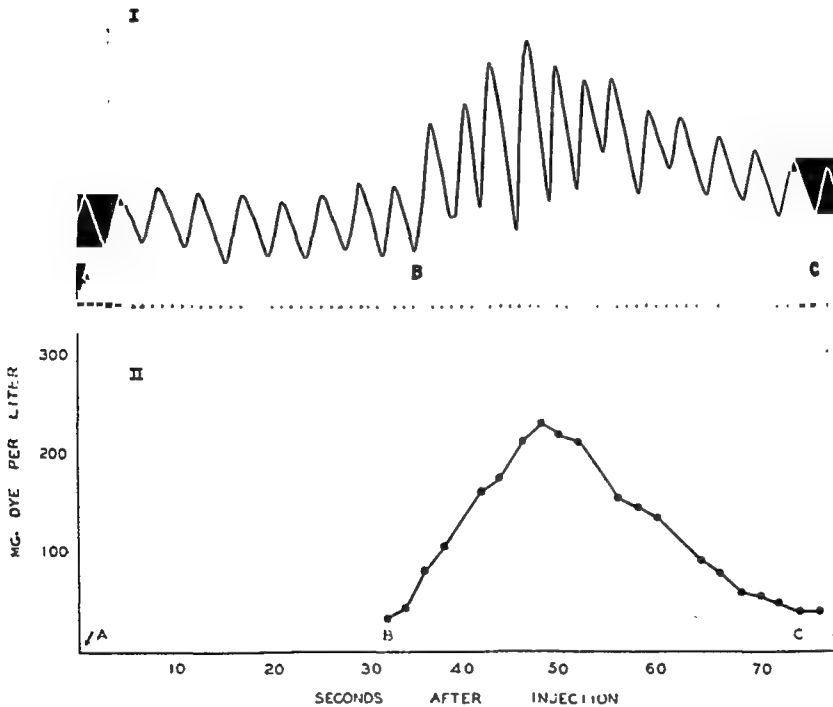


Fig. 2.—Comparison of the respiratory response to cyanide (tracing 1) with the dye distribution curve (tracing 2) in the same patient with heart disease. A, Time of injection; B, onset of respiratory stimulation (34 sec.), and appearance of dye in the femoral artery (32 sec.); C, disappearance of respiratory stimulation (74 sec.) and of the dye (74 sec.). Note the similarity of the two curves.

observed in normal subjects. Normal and pathological types of respiratory response are illustrated by the tracings in Fig. 1.

The long continued stimulation of respiration by cyanide in circulatory failure is indirect evidence of the "stringing out" of the blood stream during its passage through the heart and lungs, which was postulated by Blumgart and Weiss¹¹ and other investigators, and has recently been demonstrated by the flattening and prolongation of the vital red distribution curve.¹² The general similarity between the respiratory response to cyanide and the dye distribution curve in patients with circulatory failure (Fig. 2) suggested the employment of cyanide

for the estimation of the "mean pulmonary circulation time." While this measurement was not feasible with the cyanide method, the character of the curve reflects the character of blood flow through the lungs.

DISCUSSION

Critique of Method

The reliability of the cyanide method for measurements of the velocity of blood flow depends primarily upon the accuracy with which the arrival of the cyanide in the carotid sinus is registered by respiratory stimulation. In circulatory failure, the accumulation of blood in the pulmonary circuit and the different velocities of blood flow through the vascular areas of the lungs cause a lowering of the initial concentration of cyanide arriving in the carotid sinus, and this tends to obscure or delay the onset of the respiratory response. The hyperirritability of the respiratory center under these circumstances, however, counteracts this tendency and thus lessens or prevents erroneous prolongation of the circulation time. In order to evaluate the reliability of the cyanide method, the results obtained were compared with those obtained with the radium emanation and dye methods.

Comparison With the Radium Emanation Method.—In patients with heart disease, as in normal subjects, the results obtained with the cyanide and radium emanation methods were found to be almost identical.⁷ In patients with compensated cardiovascular disease the velocity of pulmonary blood flow as measured by both methods was found to be normal or slightly diminished, and the peripheral circulation essentially normal (Table I). In the forty-six patients with circulatory failure, on the other hand (Tables II to V), the cyanide pulmonary circulation time averaged 23.2 seconds (13 to 45 seconds), or 119 per cent longer than the normal time; while the pulmonary circulation time measured by the radium emanation method in twenty-two patients with comparable types of heart disease and comparable severity of failure averaged 26.1 seconds (14.5 to 67 seconds), or 142 per cent longer. The general correspondence of the severity of decompensation in these two groups of patients is further indicated by the reduction of the vital capacity to 1,071 and 1,349 c.c. per square meter, respectively. Measurements of the velocity of venous blood flow were also in satisfactory although less striking agreement. The average cyanide arm venous circulation time, or "venous velocity index," was 7.5 seconds (2 to 25 seconds), or 67 per cent longer than the normal time, as compared with the "arm to heart" circulation time of the radium emanation method of 14.5 seconds (4 to 31 seconds), which was an increase of 123 per cent. The shorter circulation times of the pulmonary and peripheral venous circulations obtained with the cyanide method indicate the reliability of the method.

Comparison With the Dye Circulation Time.—In normal subjects, the cyanide arm-to-carotid circulation time is in close agreement with the arm-to-femoral circulation time determined by the dye or glucose method; in eight subjects it was found to average 1.3 seconds less than the glucose circulation time.⁷ Forty determinations made with these methods in twenty-seven patients with circulatory failure revealed in general a satisfactory agreement (Tables II to V): 26.7 seconds (15 to 65 seconds) for the average cyanide circulation time; and 25.1 seconds (15 to 68 seconds) for the dye circulation time. In twenty-five determinations (with one exception) the cyanide circulation time was the greater by 1 to 6 seconds; in eight determinations it was the smaller by 1 to 4 seconds; and in seven instances no difference was detected. The more uniform concordance observed in normal subjects is not to be expected here, as the comparative determinations were made consecutively, not simultaneously, and were carried out under the slightly different experimental conditions required by each method. Case 9 (Table IV) illustrates the accuracy of the cyanide circulation time in extreme circulatory failure marked by intense dyspnea and pronounced retardation of blood flow. The cyanide circulation time was prolonged to 65 seconds; the dye circulation time measured 68 seconds.

The close correspondence of the measurements of the pulmonary circulation time obtained with the cyanide, radium and dye methods is substantial evidence that in patients with cardiovascular disease, as in normal subjects, the cyanide method provides a practical and reliable index of the velocity of pulmonary and peripheral venous blood flow.

Types of Circulatory Failure and Changes in the Hemodynamics

A correlation of the results of the circulatory measurements with the degree of disability of the patients failed to reveal a strict relationship. In general, the greater the deviation from the normal values, the more severe were the symptoms. The reverse relationship, namely, marked cardiac disability associated with great changes in the blood flow and in other aspects of the circulation, was not necessarily present.

Among the aspects of the circulation studied, the vital capacity of the lungs was the first to show a change. At times it reached a level of 50 per cent of the normal value, while the pulmonary blood flow showed only a slight degree of slowing. With more severe circulatory failure further reduction in the vital capacity of the lungs was relatively small, while the slowing of the pulmonary blood flow became rather marked. At this stage there often appeared also a decrease in the velocity of the venous blood flow and a progressive elevation of the peripheral venous pressure. These findings suggest that a relatively small amount of pulmonary engorgement can induce an appreciable reduction in the vital capacity of the lungs, while further engorgement produces proportionately little change.

We wish to call particular attention to the behavior of the circulation in two groups:

1. In several instances (Cases 1, 3, 10—Table II; Case 1—Table IV) the pulmonary circulation time remained within normal limits despite clinical, x-ray and vital capacity findings characteristic of pronounced stasis in the pulmonary circulation. The exact explanation of these findings cannot be given from available data, but there is evidence suggesting that pulmonary vascular hypertension was the responsible factor. The sharply accentuated, ringing, pulmonic second sound invariably present speaks also for exceptional pulmonary hypertension in these cases, while the values for cardiac output, pulmonary blood volume, minimal and mean pulmonary circulation time obtained with the vital red method¹⁰ denote the relative normality of blood flow through the lungs, and therefore exclude pulmonary stasis as an important factor.¹³ The inference is that the manifestations of circulatory failure, under these circumstances at least, are caused primarily by an increased pressure in the pulmonary vascular bed which induces stiffening of the lungs and extravasation of fluid from the pulmonary capillaries, without alteration of the pulmonary blood flow.

2. In a group of patients with arterial hypertension, and with syphilitic and arteriosclerotic heart disease often associated with cardiac asthma and marked disability, there occurred a reduction in the vital capacity of the lungs and a slowing of the pulmonary blood flow, but no retardation of the peripheral venous blood flow and no elevation of the venous pressure. This behavior of the peripheral blood flow was verified clinically by the rapid filling of the brachial vein following emptying, and by the absence of peripheral edema and hepatic enlargement. In several instances the venous circulation time was appreciably shortened. This latter behavior of the venous circulation may be the result of the following factors singly or combined: (a) a constriction of the peripheral veins, as observed in a number of these patients; (b) an increase in the aspiratory action of the thorax, as indicated by the inspiratory retraction of the intercostal spaces, and by the simultaneous rhythmic fall in the arterial and venous pressures; (c) an accumulation of blood in the lungs, leading to a reduction of the peripheral circulatory blood volume.

These clinical and experimental observations indicate that *failure of the pulmonary circulation alone is frequently responsible for severe disability*. In the majority of instances of circulatory failure, however, severe disturbance of the pulmonary circulation is associated with changes in the greater circulation.

SUMMARY

1. Sodium cyanide in amounts sufficient to produce adequate stimulation of respiration can safely be administered to patients with cardio-

vascular disease. The average effective dosage is approximately three-fourths that required by normal subjects: 5.2 mg., or 2.6 c.c. of a 2 per cent solution, which is equivalent to 0.084 mg. per kilogram. The fact that the respiratory center is hyperirritable to cyanide in the presence of circulatory failure makes this method particularly suitable for the measurement of the velocity of blood flow in heart disease. No untoward results have followed its administration to patients with circulatory failure when given in amounts sufficient to produce marked stimulation of respiration.

2. The curve representing respiratory response following administration of cyanide reveals the character of the pulmonary blood flow in heart disease.

3. Comparative measurements of the circulation time obtained with the cyanide, radium emanation, and vital red methods reveal that results obtained with the cyanide method are reliable indices of the velocity of blood flow in the pulmonary and peripheral venous circulations. As a rule the prolongation of the circulation time paralleled the severity of circulatory failure.

4. Marked reduction in the vital capacity of the lungs may develop at an early stage of circulatory failure when the velocity of pulmonary blood flow shows slight or no decrease and the peripheral venous circulation, as well as the venous pressure, is normal.

5. In a group of patients with arterial hypertension and intense dyspnea, evidence was obtained that pulmonary vascular hypertension existed without retardation of the blood flow through the lungs.

6. In a group of patients with disability due to hypertensive, syphilitic, or arteriosclerotic cardiovascular disease, disturbances of the pulmonary circulation were associated with normal peripheral venous circulation.

7. Owing to the numerous factors influencing hemodynamics, no strict correlation existed between clinical manifestations and the aspects of the circulation studied. Statistically, progressive reduction in the vital capacity and in the velocity of the pulmonary and peripheral venous blood flow, as well as an elevation of the venous pressure, are associated with an increasing degree of disability.

REFERENCES

1. Koch, E.: Die Strömungsgeschwindigkeit des Blutes, *Deutsches Arch. f. klin. Med.* 140: 39, 1922.
2. Blumgart, H. L., and Weiss, S.: Clinical Studies on the Velocity of Blood Flow. IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, *J. Clin. Investigation* 5: 343, 1928. VIII. The Velocity of Blood Flow and its Relation to Other Aspects of the Circulation in Patients With Pulmonary Emphysema, *ibid.* 4: 555, 1927.
3. Weiss, S., Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, *AM. HEART J.* 4: 664, 1929.

4. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis, *J. Clin. Investigation* 9: 69, 1930-1931. XIV. The Circulation in Myxedema With a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis, *Ibid.* p. 91. XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients With "Primary" and Secondary Anemia and in Two Patients With Polycythemia Vera, *ibid.* p. 679.
5. Kahler, H.: Ueber Veränderungen der Blutumlaufszeit (Ein Beitrag zum Problem der Blutgeschwindigkeit), *Wien. Arch. f. inn. Med.* 19: 1, 1929-1930.
6. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion, *Med. Klin.* 27: 986, 1931.
7. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8: 650, 1933.
8. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* 98: 475, 1910.
9. Moore, J. W., Kinsman, J. M., Hamilton, W. F., and Spurling, R. G.: Studies on the Circulation. II. Cardiac Output Determinations; Comparison of the Injection Method With the Direct Fick Procedure, *Am. J. Physiol.* 89: 331, 1929.
10. Weiss, S., and Robb, G. P.: Unreported observations.
11. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow. V. The Physiological and Pathological Significance of the Velocity of Blood Flow, *J. Clin. Investigation* 4: 199, 1927.
12. Moore, J. W., Hamilton, W. F., Kinsman, J. M., and Spurling, R. G.: Studies on the Circulation; Description of the Injection Method of Studying the Circulation With Some Clinical Applications, *Southern M. J.* 23: 1131, 1930.
13. Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure, *J. A. M. A.* 100: 1841, 1933.

PULMONARY HEART DISEASE IN PNEUMOCONIOSIS*

JOHN M. DYSON, M.D.
HAZLETON, PA.

PULMONARY heart disease, or *cor pulmonale*, is an entity characterized by right ventricular enlargement, especially marked in the out-flow tract (conus arteriosus and pulmonary artery). It results from diseases which impede the pulmonary circulation, and has been recognized at post-mortem examinations for a great many years. Schroetter¹ described it in 1876. Similarly it is referred to in most textbooks of pathology (e. g., MacCallum²) and in exhaustive treatises on heart disease (e. g., White³) where it receives adequate description of its etiology, symptomatology, diagnosis, and treatment.

The ante-mortem diagnosis of pulmonary heart disease could not be proved before the advent of the roentgen-ray and the electrocardiogram. With progress in roentgen-ray study of heart disease, however, right ventricular enlargement is now recognizable when the normal concavity on the left border of the cardiac silhouette is replaced by a bulging convexity representing enlargement of the pulmonary artery and conus arteriosus. This fundamental observation was first made by Assmann,⁴ and has been emphasized repeatedly since.^{5, 6, 3, 7, 8, 9, 10, 11} Electrocardiography further enhances the possibility of diagnosis when showing right axis deviation.

The present paper is concerned with pulmonary heart disease resulting from pneumoconiosis in anthracite coal miners—a group which inhales great amounts of carbon together with silica particles, is not particularly susceptible to tuberculosis, and achieves fair average longevity. The conclusions reached are believed applicable in this type of pneumoconiosis, but by no means should they be applied to the pure silicosis of noncarbon workers, a disease generally terminating *early* in disability and death from “silico-tuberculosis.”

Because of its industrial incidence, disabling features, and compensation potentialities, pneumoconiosis has achieved great importance. As a disease entity characterized by long-standing pulmonary fibrosis, sufficient to impede pulmonary circulation, it is urged that it be entitled to a place of its own among the potential causes of pulmonary heart disease. Furthermore, since the roentgen-ray and electrocardiogram together are now able to indicate the presence of pulmonary heart disease ante-mortem, it seems expedient to present our observations regarding its incidence and symptomatology in a series of anthracite coal miners.

*From the Medical Service of the Hazleton State Hospital.

While *cor pulmonale* has an incidence of only 0.9 per cent in Boston, as White³ states, it is not so infrequent in the hard coal regions, and should not be neglected as an oddity. Future investigations of pneumoconiosis will be far more accurate in prognosticating disability from right heart failure if the pulmonary artery shadow is understood, and if the presence or absence of right axis deviation is ascertained with the galvanometer. (If pneumoconiosis eventually becomes compensative, the economic aspect of these facts may be enormously important.)

INCIDENCE

From July, 1931, to October, 1933, 213 cases of pneumoconiosis were examined in the Hazleton State Hospital. Of these 51 (or 24 per cent) were first stage, 94 (or 44 per cent) were second stage, and 56 (or 26 per cent) were third stage cases. The classification is that of Pancoast and Pendergrass, as given by Sante.¹² Twelve cases (or 6 per cent) were unclassified since the pathologic condition was doubtful, or the probability of tuberculosis great.

In 86 patients the pneumoconiosis was probably insufficient materially to increase the resistance to the pulmonary circulation. These were generally the first or early second stage cases. In 127 patients the pneumoconiosis was marked enough to obstruct the pulmonary circulation. These were the marked second and third stage cases. Table I shows the

TABLE I
INCIDENCE

TYPE OF CARDIAC SILHOUETTE	SUFFICIENCY OF PNEUMO- CONIOSIS TO RESIST PULMONARY CIRCULATION	
	INSUFFICIENT 86 CASES	SUFFICIENT 127 CASES
Normal cardiac silhouettes	64	81
Enlargement of transverse diameter (unrelated cardiac hypertrophy)	14	17
Tortuosity, dilatation, of aorta (arteriosclerotic heart disease)	5	11
Enlargement of pulmonary artery and conus shadows (pulmonary heart disease)	0	18
Same, but from mitral stenosis	3	0
Totals	86	127
Total cases of pneumoconiosis studied: 213		

various types of cardiac silhouettes found, together with their incidences.

Pulmonary heart disease, evidenced by enlargement of the pulmonary artery and conus shadows, was found in 18 cases. The incidence, therefore was 14 per cent (18 among 127 cases) in pneumoconiosis sufficient to cause it, and 8.4 per cent (18 among 213 cases) in pneumoconiosis of all stages. Incidence based on the total number of cases of all organic heart disease (miners and non-miners) seen in the hospital during the same period is 2.9 per cent (18 among 608 cases).

INCIDENCE

TYPE OF CARDIAC SILHOUETTE	SUFFICIENCY OF PNEUMO- CONIOSIS TO RESIST PULMONARY
-------------------------------	--

TABLE II
SYMPTOMATOLOGY

CASE	AGE	YEARS		PULMONARY SYMPTOMS (COUGH, EX-PECTORATION, ASTHMA)	CARDIAC OR PULMONARY SYMPTOMS (DYSPNEA, CYANOSIS, CONGESTION)	X-RAY FINDINGS			ELECTROCARDIOGRAM	REMARKS; PRESENT CONDITION
		COAL DUST	AS MINER			STAGE PNEUMO-CONIOSIS	PROMINENT PULMONARY ARTERY	ENLARGED HEART RIGHT TO LEFT		
1. M. H.	67	20+	4+	+	++	2	yes	no	R.A.D.	Died, autopsy
2. J. K.	49	27	5	++	+	2	yes	no	R.A.D.	TB?
3. A. G.	51	30	?	+	0	3	yes	no	none made	Died, no autopsy
4. M. F.	52	10	1+	+	+	3	yes	R	R.A.D.	Disabled
5. J. G.	45	26	7	+	0	3	yes	no	R.A.D.	Disabled
6. H. C.	43	17	6	+	+	3	yes	no	R.A.D.	Disabled
7. S. C.	39	22	?	+	0	2	yes	no	R.A.D.	Working
8. J. S.	38	20	10	+	sl.	2	yes	R & L	R.A.D. Prom. P waves	Working
9. C. A.	35	17	1	+	++	2	yes	R & L	R.A.D. T ₂ change	Working
10. J. B.	57	37	0?	+	+	3	yes	no	L.A.D. T ₂ change	Disabled, sclerosis
11. W. D.	39	16	1	± sl.	+	1	yes	no	R.A.D.	?
12. I. K.	64	40	2-3	+	sl.	3	yes	no	R.A.D. Aur. fibrillation	Disabled
13. J. R.	37	21	3	+	+	2	yes	no	R.A.D. Extrasystoles?	?
14. P. P.	38	16	1+	± ?	+	2	yes	R & L	Normal	?
15. M. C.	24	4	2	0	0	2	yes	no	R.A.D.	Working
16. J. M.	52	23	1	+	+	2	yes	no	R.A.D. Prom. P waves	Disabled
17. M. M.	39	5	?	+	++	2	yes	R	R.A.D. T ₂ change	Disabled
18. J. R.	45	20	1-2	+	++	2	yes	no	Aur. Fibrillation Tendency to R.A.D. T ₂ change	?

SYMPTOMATOLOGY

In this series of 18 cases, none had histories of syphilis, and none had positive or doubtful Kahn tests. None presented a history of rheumatic fever except Case 18 (J. R.). No case presented clinical evidence of



Fig. 1.—Case 1, M. H., second stage pneumoconiosis, with pulmonary heart disease, confirmed by autopsy.

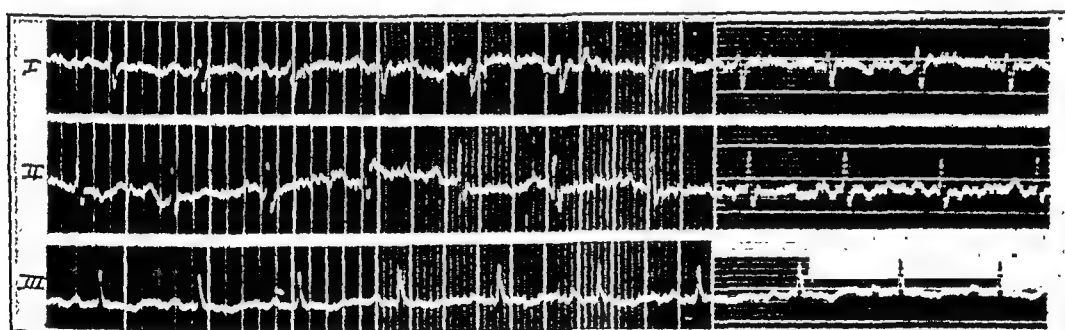


Fig. 2.—Electrocardiogram of Case 1, made two hours before death; right axis deviation.

mitral stenosis. All blood pressure readings were considered normal or subnormal for the age. Many of the cases showed a pulmonic second sound louder than the aortic. The important symptoms together with the roentgenological and electrocardiographic findings are tabulated in Table II.

The chest films, together with the electrocardiograms of 2 cases are illustrated. (Figs. 1, 2, 3, 4.) Cases 2, 3, 4, 5, and 6 were illustrated in a previous publication.¹¹ The remainder of the series have similar chest



Fig. 3.—Case 8, J. S., second stage pneumoconiosis, with enlargement of transverse diameter of the heart to right and left, and pulmonary heart disease.

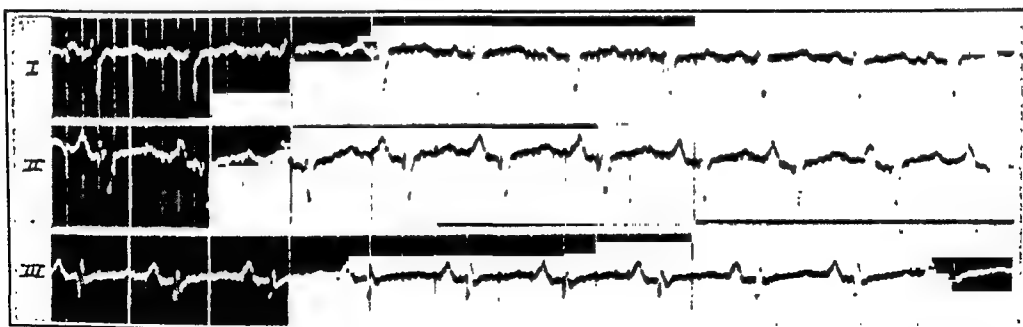


Fig. 4.—Electrocardiogram of Case 8. Right axis deviation; prominent P-waves in Leads II and III.

films. The electrocardiograms also are similar to those illustrated, with the exception of Cases 10, 14, and 18, which showed left axis deviation, normal tracing, and "right axis deviation" respectively.

Case 13 presented frequent extrasystoles. Cases 12 and 17 showed auricular fibrillation together with right axis deviation. T_1 or T_2 inversion was met with in Cases 9, 10, 17, and 18. Abnormally large P-waves were found in Cases 8 and 16. Attention is called to the fact that, while the majority of these patients are disabled, only two are known to have died.

Post-mortem examination was obtained on Case 1, M. H., who died of right heart failure. The heart weighed 450 grams. The pulmonary artery was much larger than the aorta and was greatly distended. The right chambers were enlarged. All valves were of normal structure, and their circumferences in centimeters were: aortic 9.0, pulmonic 11.5, mitral 8.7, and tricuspid 11.0. The thickness of the right ventricular wall varied between 0.7 and 1.3 cm. near the apex to 2.0 cm. at the base near the tricuspid valve. The thickness of the left ventricle did not exceed 1.9 cm. (Microscopic study showed hyperplasia and hypertrophy in the right ventricular myocardium. Pale staining was noted, and also hydropic degeneration and degenerative fragmentation.)

SUMMARY AND CONCLUSIONS

1. Pulmonary heart disease is described, together with its diagnosis by roentgenography and electrocardiography.
2. A series of 18 cases of its occurrence in pneumoconiosis is presented to illustrate incidence and symptomatology.
3. The disability and incidence indicate that pulmonary heart disease is not a rarity in anthracite coal miners, and must not be neglected.
4. It is urged that pneumoconiosis, because of its great economic and industrial importance, be more generally considered an important cause of pulmonary heart disease.
5. No attempt is made to explain why pulmonary heart disease occurs in some cases of marked pneumoconiosis, but not in others equally marked.

REFERENCES

1. Schroetter, L.: *Cyclopaedia of the Practice of Medicine*, Vol. VI, p. 196, New York, 1876, Wm. Wood & Co.
2. MacCallum, W. G.: *Textbook of Pathology*, p. 437. Philadelphia, 1925, W. B. Saunders Co.
3. White, P. D.: *Heart Disease*, pp. 404-409, New York, 1931, the Macmillan Co.
4. Assmann, H.: *Die klinische Röntgendiagnostik der inneren Erkrankungen*, Leipzig, 1928, F. C. W. Vogel.
5. Steel, D.: *Roentgenological and Pathological Findings in Valvular Lesions*, *Am. J. Roentgenol.* 23: 384, 1930.
6. East, C. F. T., and Bain, C. W. C.: *Recent Advances in Cardiology*, Philadelphia, 1931, P. Blakiston's Son & Co., Inc.
7. Nichols, C. F.: Personal communication.
8. Nemet, G.: *Some Clinical Aspects of Radiology of the Heart*, *M. Clin. North America* 15: 1392, 1932.

9. Nemet, G., and Schwedel, J. B.: Roentgenographic Studies of the Right Ventricle, *AM. HEART J.* 7: 560, 1932.
10. Roesler, H.: Roentgen-Ray Interpretation of Cardiovascular Disease, Part II, Modern Conceptions of Cardiovascular Disease, *American Heart Assn.* 11, 10, Oct., 1933.
11. Dyson, J. M.: Radiologic Recognition of Heart Disease in Pneumoconiosis, *Am. J. M. Sc.* 186: 165, 1933.
12. Sante, L. R.: *Annals of Roentgenology*. Vol. XI. The Chest, pp. 372, 373, New York, 1931, Paul B. Hoeber, Inc.

THE EFFECT OF GENERALIZED ANOXEMIA ON THE ELECTROCARDIOGRAM OF NORMAL SUBJECTS. ITS BEARING ON THE MECHANISM OF ATTACKS OF ANGINA PECTORIS*†

L. N. KATZ, M.D., W. W. HAMBURGER, M.D., AND W. J. SCHUTZ, M.D.
CHICAGO, ILL.

EVIDENCE has accumulated that characteristic changes in the S-T segment and T-wave accompany spontaneous and induced attacks of angina pectoris.¹⁻⁹ The procedures (viz., exercise, insulin, adrenalin, generalized anoxemia, etc.) employed to bring on attacks of angina pectoris in patients suffering from this disease have been found to produce the electrocardiographic changes even when they failed to cause anginal attacks.⁶⁻⁹ Furthermore these procedures have been found to cause similar electrocardiographic changes in patients without a history of angina pectoris and in normal subjects used as controls (Katz, Hamburger and Lev,⁶ Scherf and Goldhammer,⁸ and Rothschild and Kissin⁹). The number of normal subjects so studied has been limited. The present report deals with observations on a further group of seventeen normal subjects. It supports the view that electrocardiographic changes such as occur during anginal attacks can appear without being accompanied by angina pectoris.

Generalized anoxemia such as that produced in the present study, has been reported to cause shifts in the S-T segment in animals (Kountz and Gruber¹⁰ and more recently Kountz and Hammouda¹¹). Greene and Gilbert¹² reported that the T-wave in normal human subjects became flattened, diphasic or inverted as anoxemia developed. However, they did not report on the effect of anoxemia on the S-T segment. Recently, Rothschild and Kissin⁹ found a depression in the S-T segment in one of the two normal subjects they studied, and no change in the other.

METHOD

The generalized anoxemia was induced by rebreathing from a recording segment spirometer of 70 liter capacity similar to the one designed by Burlage and Wiggers;¹³ a two-way flap valve was used to direct the expired air back into the spirometer through a soda-lime container to remove the CO₂. The completeness of CO₂ removal was checked by analyzing samples of air from the spirometer with Marriott tubes.¹⁴ Before each experiment the spirometer was thoroughly aerated and then calibrated. The subject reclined comfortably on a cot during the rebreathing. Con-

*From the Heart Station, Michael Reese Hospital, Chicago.

†Aided by the Frederick K. Babson and the Emil and Fanny K. Wedeles Funds for the Study of Diseases of the Heart and Circulation.

trol electrocardiogram, blood pressure and heart rate were obtained, and these observations were repeated during the course of the anoxemia and following the resumption of breathing room air. The respiratory excursions were inscribed on a smoked paper kymograph by means of a lever moving with the rubber covered top of the segment spirometer. The excursion was calibrated in liters, and time was recorded in 5-second intervals. The minute volume of respiration was obtained from the curve by computing the product of amplitude of respiration in liters and the rate of respiration per minute; the control reading was obtained from the curve inscribed during the first minute of rebreathing. Since the expired CO_2 was absorbed before the rebreathed air was returned to the spirometer, there is a slight error in this computation.

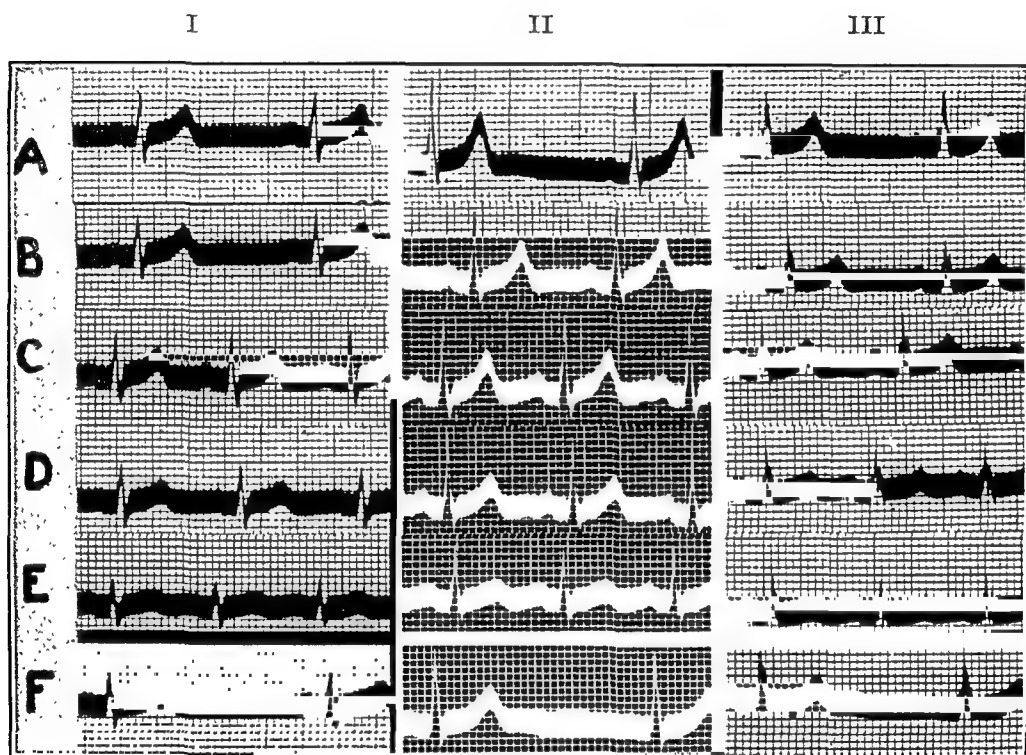


Fig. 1.—Normal subject W.S. Standard three leads of electrocardiogram during induced generalized anoxemia. Segment A, control while breathing room air. Segments B, C, D and E successive stages during rebreathing (D and E being taken in rapid succession just before end), O_2 content of inspired air being respectively about 17.8, 13.7 and 9.6 volumes per cent. Segment F was taken two minutes after resuming breathing of room air.

The level of the pointer moving with the rubber covered top of the segment spirometer was maintained constant by running in water throughout the experiment from a graduated 20 liter bottle in amounts sufficient to replace the oxygen consumed. The oxygen content at various stages of the test was computed from the quantity of water run out of the bottle at the time of estimation. As a check, a sample of the spirometer air obtained at the end of the rebreathing was analyzed with a Haldane apparatus for its O_2 and CO_2 content.

The rebreathing was terminated on signal whenever the subject felt moderately uncomfortable. However, the subject was closely watched, since events move rapidly at the critical stage and unconsciousness may develop abruptly. The duration of the rebreathing period in this series varied from twenty-five to thirty-five minutes.

RESULTS

The essential changes observed in this series of subjects are summarized in Table I, and records illustrative of the sequence of the electrocardiographic alterations are shown in Figs. 1 to 4.

It was found that during the induced generalized anoxemia, the most consistent changes in the electrocardiogram were a flattening of the T-

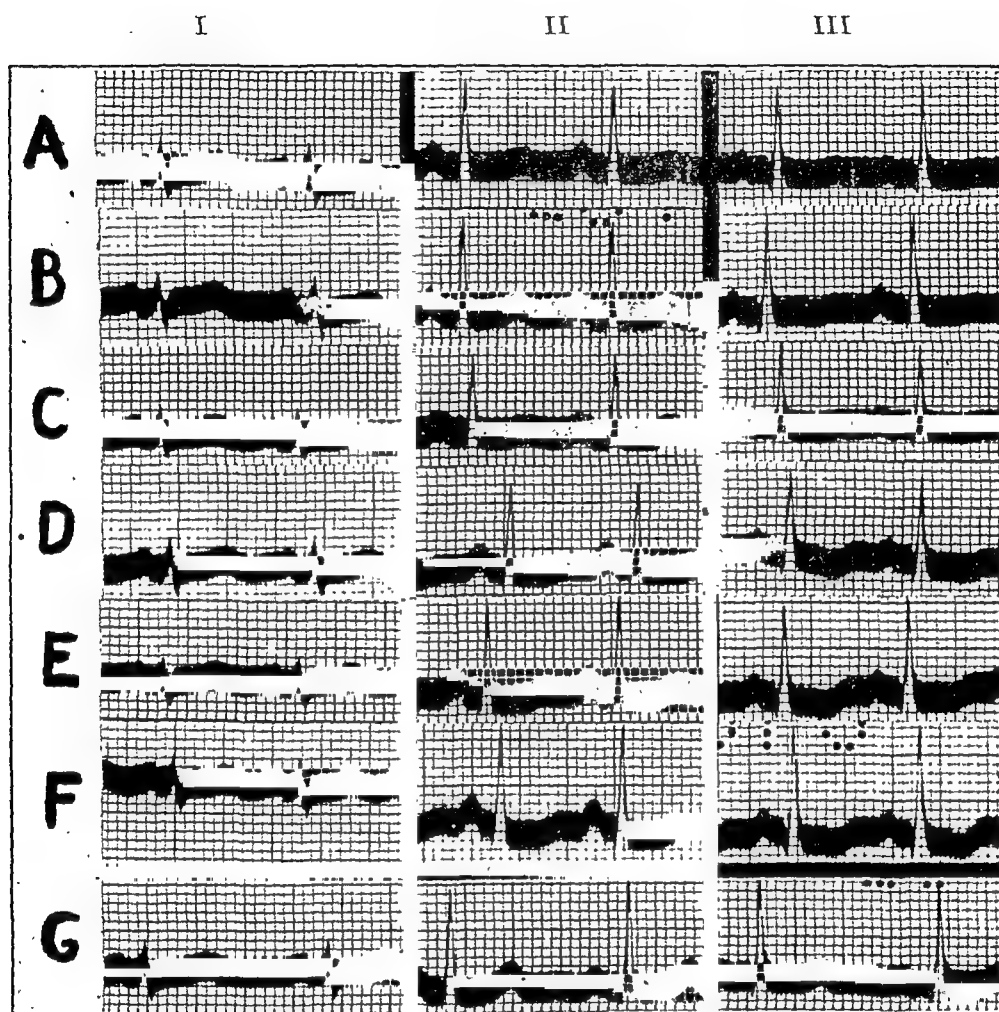


Fig. 2.—Normal subject C.M. Standard three leads of electrocardiogram during induced generalized anoxemia. Segment A, control while breathing room air. Segments B, C, D, E and F, successive stages during rebreathing (E and F being taken in rapid succession just before end), O_2 content of inspired air being respectively about 18.4, 15.8, 13.2 and 10.6 volumes per cent. Segment G was taken seven minutes after resuming breathing of room air.

wave in one or more leads, in some instances followed by its inversion (Figs. 2 and 4). In practically every instance, the level of the S-T segment tended to be shifted downward during anoxemia. Since the S-T segment in many of these subjects was definitely elevated above the isoelectric level at the start—a not uncommon finding in normal individuals—the downward shift during anoxemia resulted, in some instances, merely in the S-T segment becoming less elevated. However,

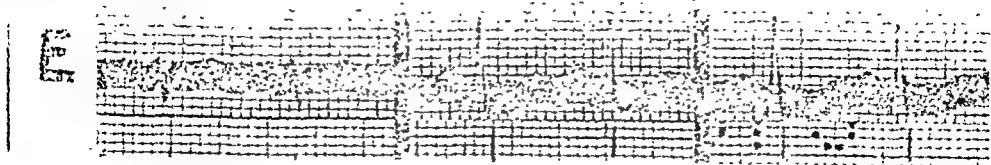


TABLE I
NORMAL SUBJECTS

SUBJECT	BLOOD PRESSURE (MM. HG)			HEART RATE (PER MIN.)			RESPIRA- TORY RATE (PER MIN.)		RESPIRA- TORY VOLUME (L. PER MIN.)		CHANGES IN P-R INTERVAL	CHANGES IN QRS AMPLITUDE	CHANGE IN LEVEL OF S-T INTERVAL			CHANGE IN AMPLITUDE OF T-WAVE MM.		
	CONTROL	END OF TEST	5 MIN. LATER	CONTROL	END OF TEST	CONTROL	END OF TEST	LEAD II	LEAD I	LEAD II			LEAD III	LEAD I	LEAD II	LEAD III		
J.P.	13.5			75	91	72	10	10	10	16	0.16 to 0.16	smaller all leads**	++ to +	+ to 0	0 to 0	+2 to +1	+1 to -1½	-1 to -½
R.S.	8.7			96	111	91	9	13	13	22	0.12 to 0.14	smaller Leads II and III	0 to 0	0 to 0	0 to 0	+1½ to +1	+2 to +1½	+1 to +½
H.G.	9.5			86	107	83	20	19	10	23.5	0.18 to 0.20	no change	+ to 0	0 to 0	0 to 0	+2 to +1	+2½ to +1	+½ to ±0
D.K.	11.3			75	94	72	17	19	8.5	19	0.16 to 0.18	smaller all leads	+ to 0	+ to 0	0 to -	+1½ to +1	+2½ to +1½	+1 to +1
W.S.	9.6			60	103	56	19	25	13	22	0.14 to 0.18	smaller all leads	+ to 0	+ to 0	+ to 0	+3 to +1	+6 to +1½	+3 to +½
J.R.*	8.5			79	130	70	15	18	7.5	11	0.14 to 0.14	smaller all leads	0 to -	+ to -	0 to -	+1 to +½	+1 to ±0	+½ to -2
C.M.*	10.6			94	115	83	14	19	11	14	0.16 to 0.14	smaller all leads (slightly)	+ to 0	0 to -	0 to -	+1½ to +1	+1 to ±0	+½ to ±0
E.S.*	12.6	125/80	130/80	72	111	68	17	29	10.5	43.5	0.14 to 0.14	smaller all leads	0 to 0	0 to 0	0 to -	+1½ to +½	+2 to +½	+1 to +½
P.B.*	9.8	120/65	125/45	83	125	79	12	23	7	14.5	0.12 to 0.12	no change	0 to 0	0 to -	0 to -	+2 to +½	+3 to ±0	+1 to ±0
W.M.	8.5	135/80	160/55	100	125	96	13	40	10	32	0.18 to 0.18	smaller all leads	+ to -	+ to -	0 to -	+½ to +½	+4 to +1	+2 to +½
G.J.	7.1	120/75	165/70	60	125	60	8	27	8	27	0.14 to 0.12	smaller all leads	+ to 0	+ to -	0 to -	+2 to +1	+2½ to +½	+½ to ±0
K.J.	6.6	145/85	165/80	83	143	88	7	19	11	57	0.16 to 0.16	smaller all leads	0 to -	0 to -	0 to -	+1½ to +½	+2½ to +1	+1 to +½

TABLE I—CONT'D

SUBJECT	INSPIRED O ₂ AT END OF TEST (VOL. %)	BLOOD PRESSURE (MM. HG)			HEART RATE (PER MIN.)			RESPIRATORY RATE (PER MIN.)		RESPIRATORY VOLUME (L. PER MIN.)		CHANGES IN P-R INTERVAL	CHANGES IN QRS AMPLITUDE	CHANGE IN LEVEL OF S-T INTERVAL			CHANGE IN AMPLITUDE OF T-WAVE MM.		
		5 MIN. LATER			5 MIN. LATER			END OF TEST		END OF TEST				LEAD II	LEAD I	LEAD III	LEAD I	LEAD II	LEAD III
		CONTROL	END OF TEST	5 MIN. LATER	CONTROL	END OF TEST	5 MIN. LATER	CONTROL	END OF TEST	CONTROL	END OF TEST								
H.K.	9.9	130/55/125/40	135/65	73	107	66	14	17	8	15	0.20 to 0.20	smaller all leads	+ to -	0 to -	- to -	+3 to + $\frac{1}{2}$	+3 to +1	+1 to + $\frac{1}{2}$	
L.R.	9.3	110/70/130/0	110/70	79	115	70	19	17	9.5	16	0.16 to 0.16	smaller all leads	+ to 0	+ to -	+ to 0	+2 to +1	+4 to +1 $\frac{1}{2}$	+2 to + $\frac{1}{2}$	
A.S.	10.1	120/90	125/80	83	100	70	18	18	9	18	0.16 to 0.16	smaller all leads	0 to 0	0 to 0	0 to 0	+1 to + $\frac{1}{2}$	+1 to + $\frac{1}{2}$	- $\frac{1}{2}$ to + $\frac{1}{2}$	
R.L.	9.1	145/80	140/70	150/95			10	18	11	27									
J.L.	10.5	125/75	130/90	110/80			14	19	11.5	39									

PATIENTS WITH A HISTORY OF ANGINA PECTORIS																			
A.F.†	8.7	120/80	115/70	110/80	100	107	88	22	20	14	27	0.18 to 0.18	smaller Leads I and III††	+ to +	+ to +	0 to 0	-1 to - $\frac{1}{2}$	-1 to ± 0	+ $\frac{1}{2}$ to + $\frac{1}{2}$
T.P.	9.0†	145/90	145/100	150/95	91	115	93	16	20	12	20	0.16 to 0.16	smaller Leads I and II larger Lead III	0 to -	0 to -	0 to 0	+ $\frac{1}{2}$ to + $\frac{1}{2}$	+1 to +1 $\frac{1}{2}$	+ $\frac{1}{2}$ to + $\frac{1}{2}$
L.F.†	10.4	180/106	168/100	184/104	115	125	107	20	14	11	29	0.18 to 0.18	smaller all leads	- to -	- to -	- to -	+1 to +1	+2 to +1 $\frac{1}{2}$	+1 to +1 $\frac{1}{2}$
W.A.	7.6	206/106	216/124	204/108	79	107	79	17	21	13	21	0.14 to 0.12	smaller all leads**	- to -	- to -	- to -	-3 to -2	-2 to -3	+1 to + $\frac{1}{2}$
M.F.†	8.1	180/116	216/120	184/112	72	91	72	13	15	10.5	24	0.14 to 0.14	smaller all leads**	- to -	0 to -	+ to -	+1 to +1	+2 to +1	+1 to ± 0
J.F.†	13.2	160/80	178/90	160/80	100	107	94	18	19	7	9.5	0.16 to 0.16	smaller all leads**	- to -	- to -	+ to +	+1 to + $\frac{1}{2}$	+1 $\frac{1}{2}$ to +1 $\frac{1}{2}$	+ $\frac{1}{2}$ to +1

*Female.	**QRS ₂ inverted.	†Developed no pain.	††QRS ₂ and ₃ inverted.
----------	------------------------------	---------------------	---

*Female.

**QRS₂ inverted.

†Developed no pain.

††QRS₁ and ₂ inverted.

in many instances the S-T segment actually became isoelectric or was depressed below the isoelectric level.

The changes in the T-wave and in the S-T segment were progressive in character and developed gradually as the oxygen in the inspired air

I

II

III

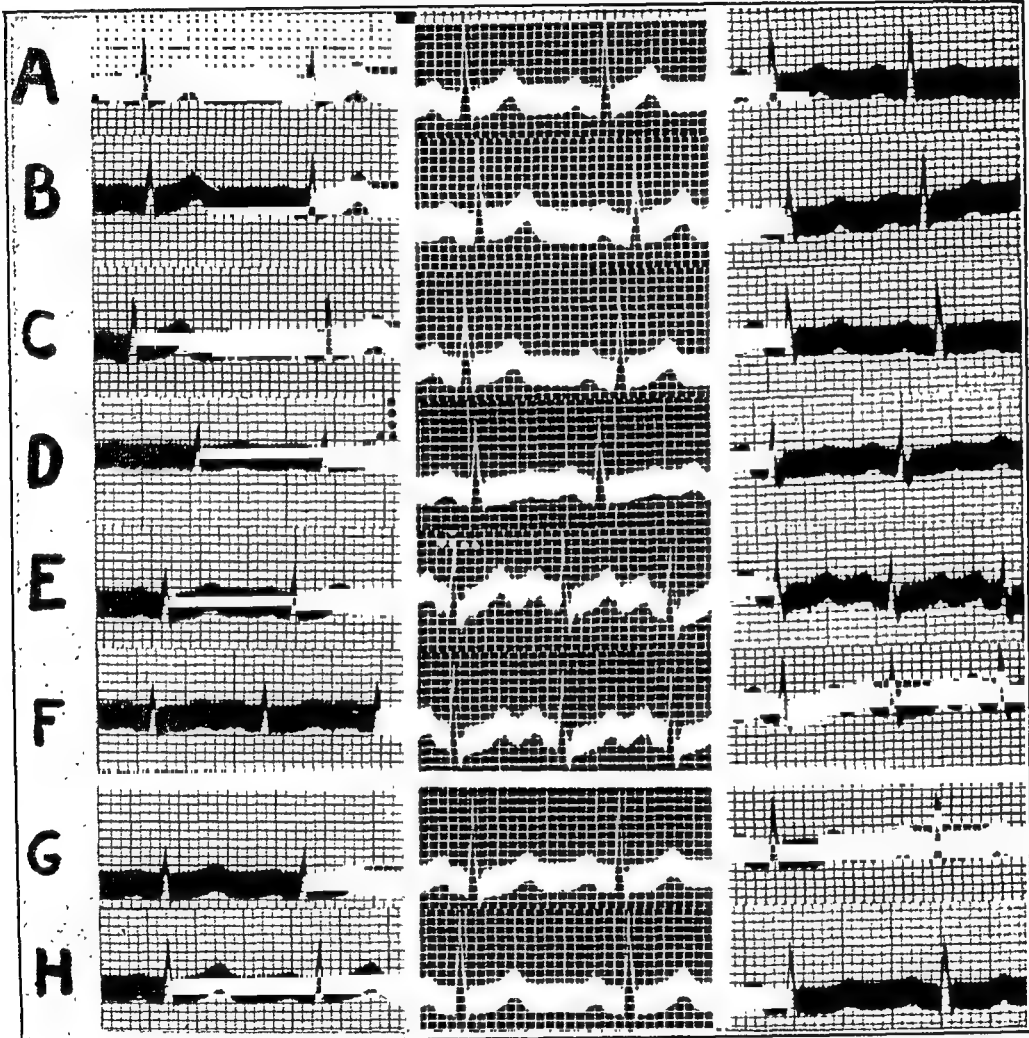


Fig. 3.—Normal subject K.J. Standard three leads of electrocardiogram during induced generalized anoxemia. Segment A, control while breathing room air. Segments B, C, D, E and F, successive stages during rebreathing (E and F being taken in rapid succession just before end). O_2 content of inspired air being respectively about 17.4, 13.8, 10.2 and 6.6 volumes per cent. Segments G and H were taken three and seven minutes respectively after resuming breathing of room air.

fell. The maximum effect was observed when the oxygen content was at its lowest level. However, the effect of anoxemia was not equally marked in all the subjects.

The contour of the electrocardiogram tended to return toward normal without much lag as soon as the subject resumed breathing room air:

DISCUSSION

The electrocardiographic changes produced in this series of normal subjects by generalized anoxemia resemble those occurring during spontaneous or induced attacks of angina pectoris. It is important to stress

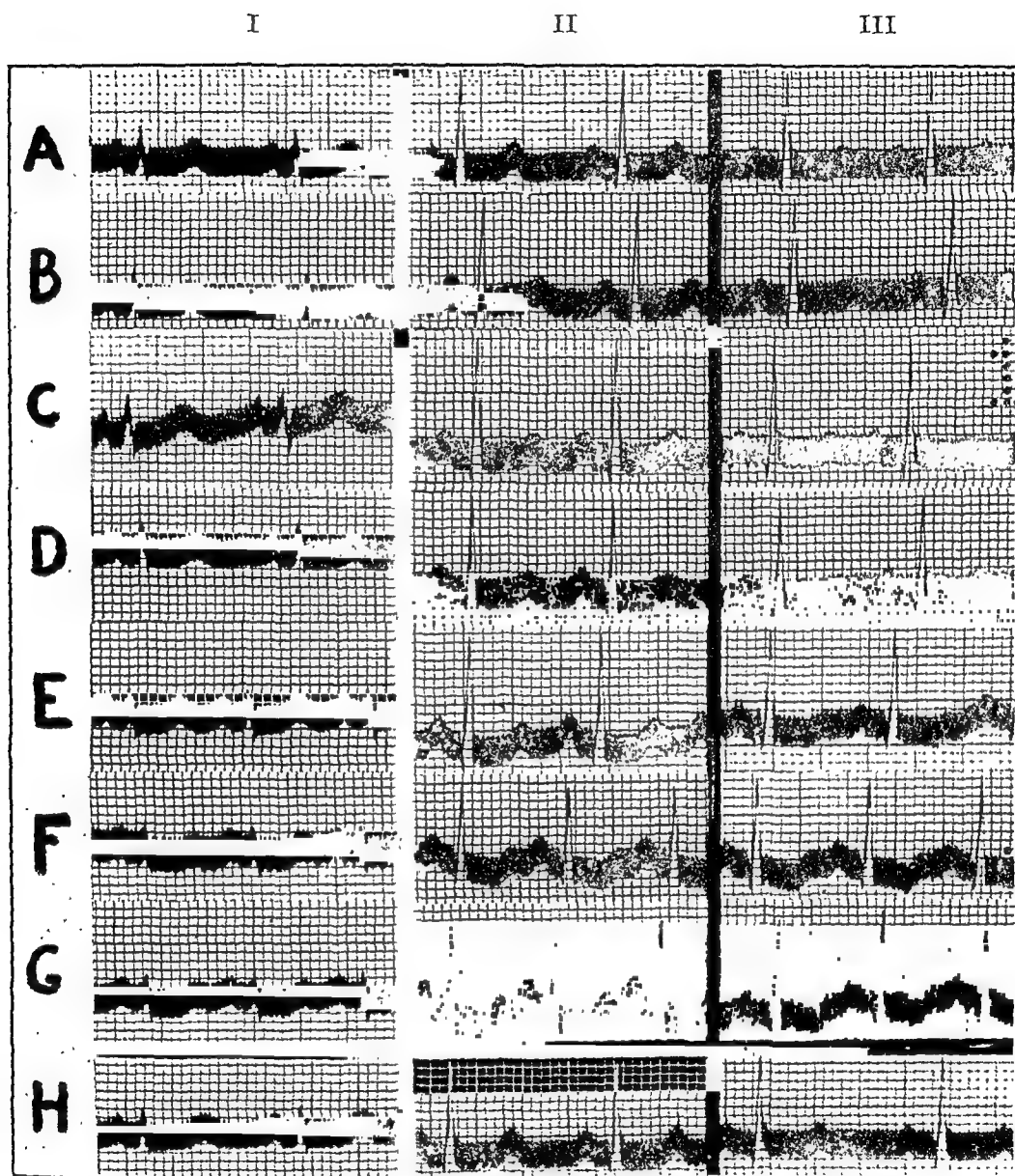


Fig. 4.—Normal subject J.R. Standard three leads of electrocardiogram during induced generalized anoxemia. Segment A, control while breathing room air. Segments B, C, D, E, F and G, successive stages during rebreathing (F and G being taken in rapid succession just before end). O_2 content of inspired air being respectively about 18.5, 16.0, 13.5, 11.0 and 8.5 volumes per cent. Segment H was taken four minutes after resuming breathing of room air.

that these electrocardiographic changes occurred without any symptoms of precordial distress. The rebreathing in every instance was stopped at command of the subject, because of discomfort or when the patient became unconscious. (This latter event occurred in only a few subjects.)

In 6 patients suffering from angina pectoris, who were tested in the same way as the normal subjects, 4 developed electrocardiographic changes similar to those observed in the normal subjects without the appearance of precordial distress. The frequency of precordial pain in this small series of angina pectoris cases is less than that reported by Rothschild and Kissin.⁹

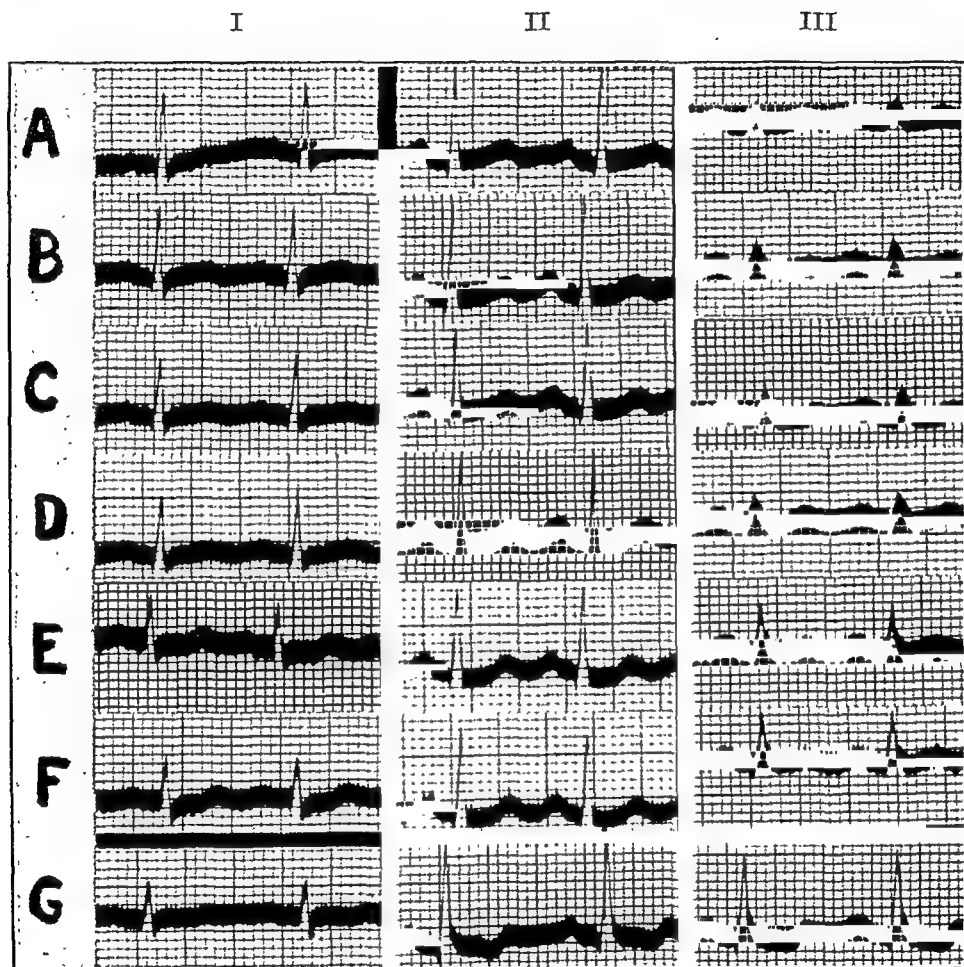


Fig. 5.—Subject T.P. (angina pectoris). Standard three leads of electrocardiogram during induced generalized anoxemia after which patient developed anginal pain. Segment A, control while breathing room air. Segments B, C, D, E and F, successive stages during rebreathing (E and F being taken in rapid succession just before end), the O_2 content of inspired air being respectively approximately 18.0, 15.0, 12.0 and 9.0 volumes per cent. However, no analysis of inspired air was made at end of rebreathing. Segment G was taken five minutes after resuming breathing of room air. Note the right axis shift in this patient which persisted and increased even after breathing of room air was resumed; the record taken after resuming breathing of room air shows other abnormalities.

Our results emphasize the fact that while anoxemia (and cardiac ischemia) consistently tends to produce characteristic electrocardiographic changes, it does not lead inevitably to attacks of anginal pain. It has been definitely established by work in this laboratory by Kissin¹⁵ and Perlow, Markle and Katz¹⁶ that generalized anoxemia will cause pain in an exercising normal skeletal muscle. There is also no doubt

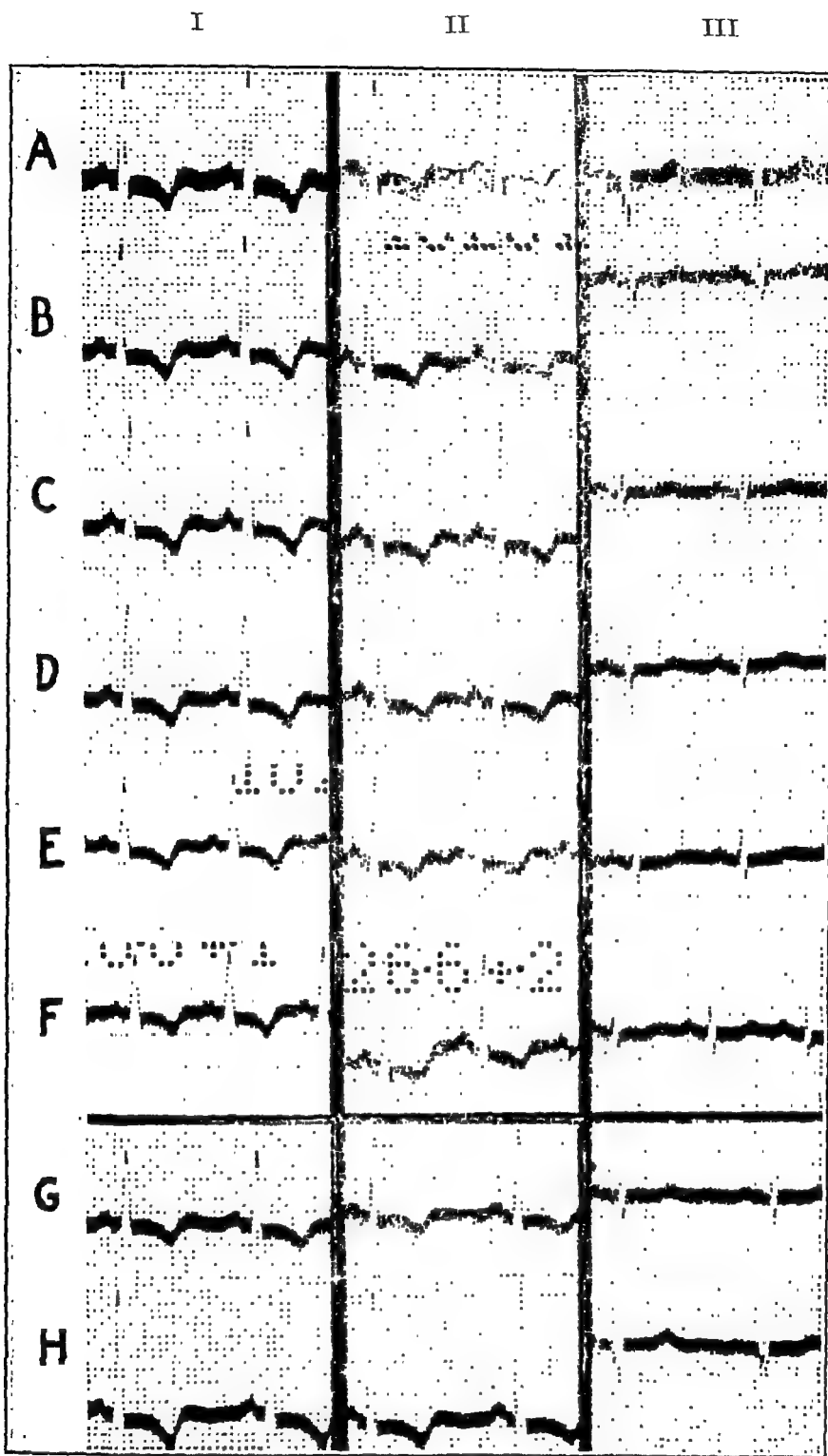


Fig. 6.—Subject W.A. (angina pectoris). Standard three leads of electrocardiogram during induced generalized anoxemia during which patient developed anginal pain. Segment A, control while breathing room air. Segments B, C, D, E and F, successive stages during rebreathing, O_2 content of inspired air being respectively approximately 18.4, 15.7, 13.0, 10.3 and 7.6 volumes per cent. Segments G and H were taken four and thirty minutes respectively after resuming breathing of room air.

that generalized anoxemia may precipitate an attack of angina pectoris in patients suffering from this disease, as was shown by Rothschild and Kissin⁹ and Dietrich and Schwegk¹⁷ and in two of the patients tested

by us. Nevertheless, generalized anoxemia as severe as the above fails to produce attacks of anginal pain in normal subjects and in some patients suffering from angina pectoris, even though the electrocardiographic changes produced resemble those seen where attacks of angina pectoris are brought on by anoxemia. Some other process besides anoxemia (or ischemia) therefore seems to be required for the appearance of attacks of anginal pain. This factor is absent during the time of re-breathing in the normal subjects and in some of the patients with angina pectoris.

It seems to us that this variable is the condition of the nervous system, either of the end organs in the heart, of the afferent pathways to the brain, or of the sensorium of the subject. Our knowledge at present is too meager to define with any degree of accuracy what factors are concerned in affecting these parts of the nervous system. This variable factor prevents the accurate prediction of the occurrence of pain during generalized anoxemia in patients suffering from angina pectoris.

Since pain is not always induced by generalized anoxemia in patients with angina pectoris, apparently this is not an accurate test for this disease. The induction of severe generalized anoxemia throws an undue strain on the heart, especially in patients with cardiac disease, and may be a serious hazard to the patient. The procedure gives diagnostic information in only a small proportion of the cases of angina pectoris and should be undertaken in patients with heart disease only with full realization of the risk involved.

SUMMARY

It was found that the induction of generalized anoxemia in normal subjects produced a diminution in the amplitude of the T-wave, at times leading to its inversion. At the same time the S-T segment was depressed and at times became negative. Similar changes were produced by generalized anoxemia in patients suffering from angina pectoris. These electrocardiographic changes occurred without the appearance of anginal pain in the normal subjects and in four of six patients suffering from angina pectoris. However, two of the six patients with angina pectoris did develop typical mild anginal pain.

It is therefore concluded that some process in addition to anoxemia (or ischemia) is concerned in the production of the pain of angina pectoris. This process is a variable which prevents the accurate prediction of the occurrence of pain during induced anoxemia. Because of the variability in the results and of the hazard to the patient, the use of induced anoxemia as a test for the presence of angina pectoris is of questionable value.

We are indebted to the volunteers who acted as subjects for this study.

REFERENCES

1. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
2. Levy, J. R.: Valeur Semiologique des Alterations du Complexe Ventriculaire Electrique dans les Syndromes Angineux, *Arch. d. mal. du coeur* 22: 513, 1929.
3. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris; Their Bearing on the Origin of Anginal Pain, *Lancet* 1: 15, 1931.
4. Wood, F. C., Wolferth, C. C., and Livezey, M. M.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attacks and Their Comparison With the Effects of Experimental Coronary Occlusion, *Arch. Int. Med.* 47: 339, 1931.
5. Siegel, M. L., and Feil, H.: Electrocardiographic Studies During Attacks of Angina Pectoris and of Other Paroxysmal Pain, *J. Clin. Investigation* 10: 795, 1931.
6. Katz, L. N., Hamburger, W. W., and Lev, M.: The Diagnostic Value of Epinephrine in Angina Pectoris, *AM. HEART J.* 7: 371, 1932.
7. Soskin, S., Katz, L. N., Strouse, S., and Rubinfeld, S. H.: Treatment of Elderly Diabetic Patients With Cardiovascular Disease. Available Carbohydrate and the Blood Sugar Level, *Arch. Int. Med.* 51: 122, 1933.
8. Scherf, D., and Goldhammer, S.: Zur Frühdiagnose der Angina pectoris mit Hilfe des Elektrokardiograms, *Ztschr. f. klin. Med.* 124: 111, 1933.
9. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.
Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 745, 1933.
10. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
11. Kountz, W. B., and Hammouda, M.: The Effect of Asphyxia and of Anoxemia on the Electrocardiogram, *AM. HEART J.* 8: 259, 1932.
12. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension; Changes in the Pace-Maker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, *Arch. Int. Med.* 27: 517, 1921.
13. Burlage, S. R., and Wiggers, C. J.: A Segment Respirometer for Studying the Effects of CO₂ in Man, *Am. J. Physiol.* 72: 192, 1925.
14. Marriott, W. M.: The Determination of Alveolar Carbon Dioxide Tension by a Simple Method, *J. A. M. A.* 66: 1594, 1916.
15. Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, *J. Clin. Investigation* 13: 37, 1934.
16. Perlow, S., Markle, P., and Katz, L. N.: Factors Involved in the Production of Skeletal Muscle Pain, *Arch. Int. Med.* (in press).
17. Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina Pectoris, *Klin. Wchnschr.* 12: 135, 1933.

ELECTROCARDIOGRAPHIC OBSERVATIONS ON THE CAROTID SINUS REFLEX

LOUIS H. SIGLER, M.D.
BROOKLYN, N. Y.

THE electrocardiographic manifestations of direct vagal stimulation have been studied experimentally in animals by Rothberger and Winterberg,¹ Einthoven and Wieringer,² Cohn,³ Lewis,⁴ and others. Although their observations varied somewhat in detail, in the main their conclusions were the same. The usual findings were sinus slowing, sino-auricular standstill and varying degrees of heart-block, from mere delay to complete dissociation. Occasionally, shifting of the pacemaker from the upper to the lower end of the sinus node was observed. Ectopic foci of impulse formation developed in some cases, resulting in auricular or ventricular escape from vagal inhibition. The ventricular portion of the conduction apparatus was rarely influenced by vagal stimulation. Increased height of the R-wave and diminished height of the T-wave were occasionally induced. In general the right vagus nerve had its main effect on the inhibition of the impulse formation, while that of the left was on the auriculoventricular conduction.

Comparatively few electrocardiographic studies of the vagal effect upon the human heart are recorded in the literature. The findings of those reported are in general the same as those seen in experimental animals. Robinson and Draper⁵ induced vagal effect by "pressure on the vagus nerve in the neck." They found inhibition to the impulse formation and occasional increase in the R-wave to be the usual right pressure effects. Left effects were mainly those of delay in auriculo-ventricular conduction, and occasional decrease in the R-wave. The T-wave was slightly flattened. No significant changes were found in the P-wave. Levine⁶ induced his vagal effect by the oculocardiac reflex. Pressure on the right eye induced occasional changes in the P-wave with frequent inhibition of the sino-auricular node. Pressure on the left had more effect on the auriculoventricular conduction. Wilson⁷ reported a case showing abnormal ventricular complexes and nodal rhythm on vagal stimulation. I⁸ reported a case of partial bundle-branch block in which reflex vagal stimulation produced normal ventricular complexes. This was attributed, however, to slowing of the heart with its resultant recuperative effect on the interventricular conduction apparatus and not to direct effect of the vagus on that apparatus. Laslett⁹ found no marked difference in the effects of the two nerves. Slowing occurred in the proportion of 68 to 55 for right and left nerves respectively. Prolonged conduction occurred in the proportion of 15 to 23 for the right

and left nerves. Kleeman's¹⁰ findings were about the same. Ritchie¹¹ found the inhibitory effect of the left vagus to be less than that of the right, both on rate and on conduction, in a case of auricular flutter with transient fibrillation.

In previous communications^{12, 13, 14} I reported the results of a clinical study of the carotid sinus reflex in a series of 345 cases. Electrocardiograms were made on a number of these cases immediately before and during the time the reflex was induced. This paper deals with an analysis of fifty representative electrocardiograms in this series. The reason why the findings in only 50 cases are reported, is that only these cases had been observed for a considerable length of time. Each had had at least two electrocardiographic examinations on previous occasions and one just before the carotid sinus reflex was elicited. This precaution was taken to rule out the possibility of any electrophysiological disturbances that might have occurred without the reflex. In each case, the electrocardiographic effects of the reflex were immediate and definite and lasted only during the period such reflex was induced. A response could be produced in each case only by the reflex.

ANALYSIS OF FINDINGS

Each electrocardiogram was obtained first in the three standard leads before carotid sinus pressure. The lead showing the highest deflection was then chosen for study of the effects of such pressure. About 8 to 12 deflections were recorded for each of the right and left vagal effects. In the majority of cases only the first 8 deflections showed any deviations from the original tracing. In each tracing obtained before and after carotid sinus pressure, the interauricular and interventricular time intervals and auriculoventricular conduction time were calculated. Likewise, the new rhythm and any new features that developed were noted. Thus any auricular and ventricular slowing, acceleration, auriculoventricular conduction disturbances and other abnormalities could be seen at a glance from the figures obtained. The findings obtained by carotid sinus pressure were further classified according to the form of disturbance of impulse formation and conduction and the changes that occurred in the auricular and ventricular complexes. Table I is a summary of this classification.

The predominant vagal effect obtained was slowing of the entire heart. In this respect left carotid sinus pressure showed more frequent response than did the right. Complete stoppage of the heart occurred twice as frequently with right as with left carotid sinus pressure. Mild grade auriculoventricular block occurred as frequently with right as with left carotid sinus pressure. High degree block (Fig. 1) occurred more than twice as frequently with left carotid pressure as with right. A curious finding was a shortening of the auriculoventricular conduction

time, which was obtained twice with right and once with left pressure effect. Variations in the normal auriculoventricular conduction time even in the same case were frequent. This occurred about three times as often with right as with left carotid sinus pressure. Ventricular escape from inhibition (Fig. 5) as well as nodal rhythm (Fig. 3) were occasionally observed. Sinus arrhythmia associated with sinus slowing was an occasional finding (Fig. 2).

TABLE I
SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS OBTAINED IN RIGHT AND LEFT
CAROTID SINUS PRESSURE

	RIGHT	LEFT
<i>Sinus Slowing</i> —Simple	14	14
With S. A.	5	7
With A-V. B.	2	3
With A-V. B. and V. E.		2
With S. A. and A-V. B.	1	2
<i>Total Showing Sinus Slowing</i>	22	28
<i>S-A. Standstill and Sinus Slowing</i>	10	3
With S. A.	5	
With N. R.	2	2
With V. E.	2	1
With A-V. B.	1	4
<i>Total Showing S-A. Standstill</i>	20	10
<i>A-V Conduction</i>		
Variations, but within normal limits	20	6
Diminished	2	1
Prolonged and variable	4	4
High degree block	5	12
CHANGES IN COMPLEXES		
<i>P-Wave</i>		
Diminished	10	5
Nearly isoelectric	5	7
Negative	1	1
Notched	1	
<i>R-Wave</i>		
Increased	6	3
With decreased S-wave	1	
Decreased	4	3
Prolonged QRS		2
<i>R-T and S-T Segment rounding or depression</i>	3	1
<i>T-Wave</i>		
Increased	1	
Decreased	1	3
Premature Contraction	2	3
Shifting Pacemaker	1	

The figures show the number of cases with respective responses. Some cases showed response to both right and left pressure. Others showed one type of response on right, and another type on left pressure. Still others showed only one-sided response.

S. A. = sinus arrhythmia.

V. E. = ventricular escape.

A-V. B. = auriculoventricular block.

N. R. = nodal rhythm.

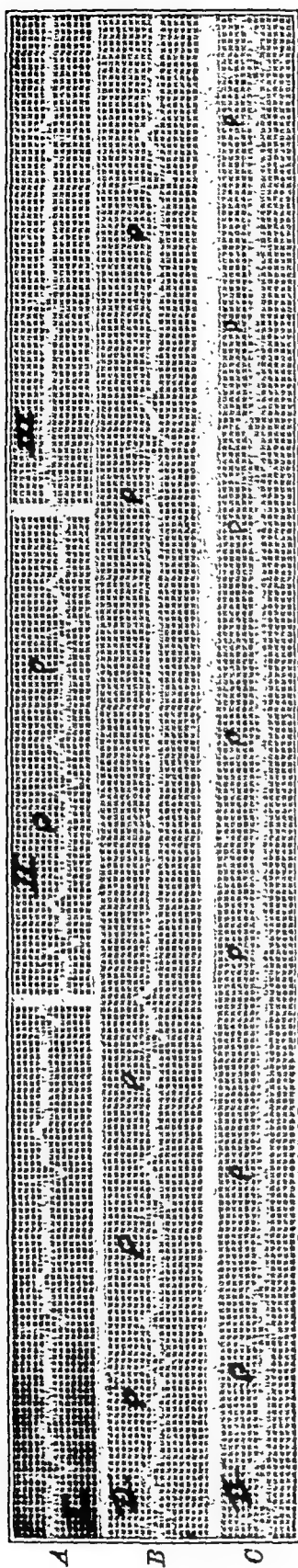


FIG. 1.-A, Tracing in the first, second, and third leads obtained before carotid sinus pressure was applied. Low voltage, slurred and notched QRS. Delay in auriculoventricular and interventricular conduction time.
 B, Second lead on right carotid sinus pressure. Sino-auricular standstill, sinus slowing and slight increase in delay of auriculoventricular conduction time.
 C, Same lead on left carotid sinus pressure. Slight sinus slowing with complete auriculoventricular block followed by increase in delayed conduction.



FIG. 2.—Obtained on left carotid sinus pressure. Sinus slowing and sinus arrhythmia. Delay in auriculoventricular conduction time in various degrees. Variations in shape and size of P-waves.

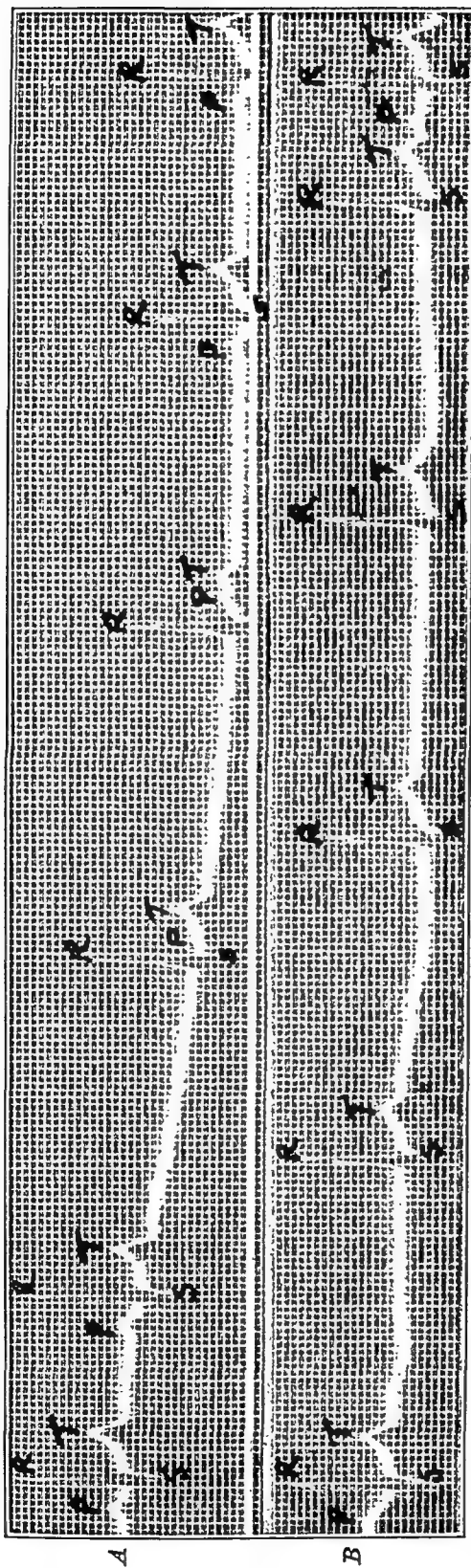


Fig. 3.—Tracing obtained on right (A) and left (B) carotid sinus pressure. A shows two normal complexes followed by two complexes of nodal origin. There is then a resumption of the regular sinus rhythm at a slower rate than previously. The R-waves are shorter. B shows sino-auricular standstill which lasted about 7.68 seconds with four ventricular complexes of nodal origin. The first of the auricular and ventricular complexes following the nodal rhythm occurs prematurely with delay in auriculoventricular conduction time.

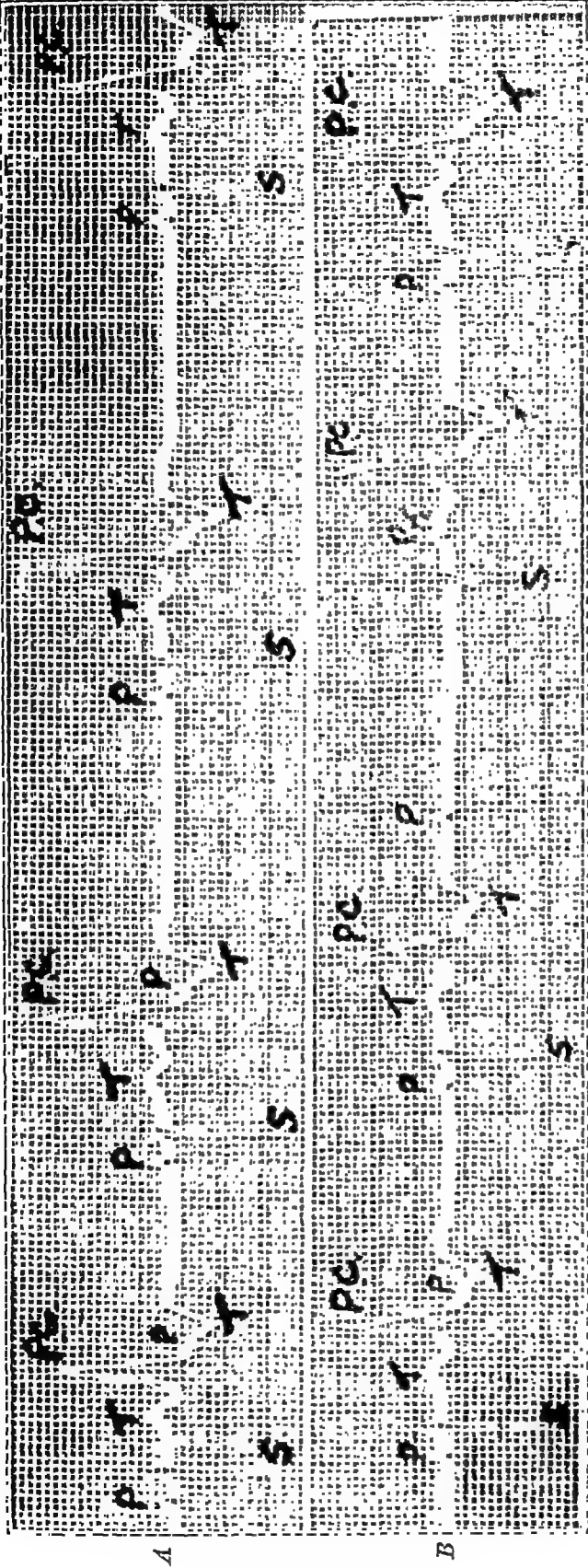


Fig. 4.—Complexes obtained on right (A) and left (B) carotid sinus pressure. A, Every normal ventricular complex is followed by a ventricular premature contraction. There is a gradually increasing sinus slowing with the auricular waves falling on the ventricular premature contractions in the first two complexes. B, Sinus slowing is less marked and auriculoventricular block occurs after the second premature contraction; there is then a ventricular complex of supraventricular origin with auricular impulse of sinus origin following it.

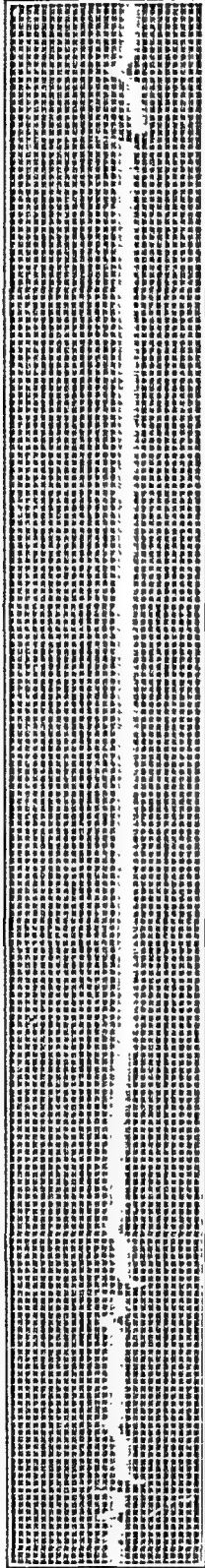


Fig. 5.—Tracing obtained on right carotid sinus pressure. Sino-auricular standstill for 7.6 seconds with ventricular escape. Diminished R-wave and increased T-wave following standstill.



Fig. 6.—Tracing obtained on left carotid sinus pressure. Sinus slowing, sino-auricular standstill, and auriculoventricular block.

Changes in the auricular complexes were rather frequent. These varied from mere lowering in voltage of the P-wave to its almost entire disappearance. Occasionally the P-wave became negative (Fig. 7) or notched (Fig. 6). These changes occurred somewhat more often on right than on left carotid sinus pressure. The variations in the P-wave usually occurred for only from one to five deflections and were more frequent after sinus standstill.

Changes in the initial ventricular complexes occurred less frequently. The R-wave was almost as often decreased as increased, and either change was slightly more frequent on right than on left sinus pressure. R-wave changes occurred usually after a prolonged standstill. Changes in the R-T and S-T segments as well as in the T-wave occurred very rarely and were slight in degree. They usually followed changes in the R-wave.

Ventricular premature contractions were noticed twice on right and

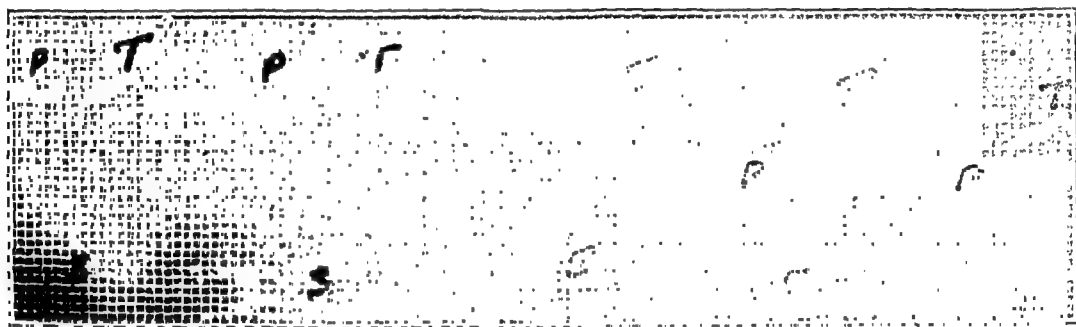


Fig. 7.—Tracing obtained on left carotid sinus pressure. The first two impulses are of normal sinus origin. The last three are of an ectopic origin.

twice on left carotid sinus pressure. In one case there occurred a sinus premature contraction on left carotid sinus pressure (Fig. 3 B).

Pulsus bigeminus was produced in one case (Fig. 4 A and B) when the rate slowed. This case, however, had shown this abnormality once before, without carotid sinus pressure. The accompanying disturbances in impulse formation and conduction had never occurred before. In two cases of auricular fibrillation carotid sinus pressure produced auriculoventricular block with ventricular slowing or standstill. The fibrillation was not influenced by such pressure.

COMMENT

The observations presented in this paper confirm previous reports of the similarity in the vagal effects on the human and on animal hearts. The main effects are those of interference with the impulse formation in the sino-auricular node and its propagation along the auricles and conducting apparatus. Although the vagal effects are reflex in origin, and we cannot therefore accurately gauge in this way the relative right and left effects, the similarity of response in humans to that obtained by

direct vagal stimulation in animals leads us to believe that the predominant reflex effect is homolateral. If this be correct, our findings indicate that both the formation and propagation of the impulse are controlled by both vagi alike, the difference being only in degree. Apparently right vagal terminals are found in greater number in the sinus node, and left terminals in the auriculoventricular nodal area. Both vagal endings are, however, found in both locations. The variations in form of response in different individuals apparently depend upon differences in the distribution of the vagal endings in the respective hearts. Anatomical, physiological, and chemical disturbances at the terminals of the vagal endings may also play a part in influencing the response. The disturbances in the appearance of the auricular complexes observed in many cases on vagal stimulation are undoubtedly due to focal interference with the normal impulse propagation along the auricles, and imply the presence of vagal terminals in the auricular walls in varying numbers.

The ventricular complexes are affected apparently little by the vagal impulses. Our findings do not corroborate those of Robinson and Draper,⁵ who report an increased R-wave on right and a decreased one on left vagal stimulation. No prediction can be made as to the character of the R-wave obtainable by vagal stimulation. Changes in the R-T and S-T segments were not described by any of the authors mentioned in this paper. We found such changes only in four instances. The T-wave is likewise very seldom affected. Although Garey¹⁵ produced the appearance and disappearance of the T-wave by local application of atropin to the various parts of the ventricles, reflex vagal stimulation affects the T-wave very little. This may be due to comparatively few vagal nerve endings in the ventricular walls of most individuals and the inability to influence conduction in the greater muscle mass of the ventricles in most cases.

SUMMARY

Fifty electrocardiograms obtained on carotid sinus pressure showed the predominant vagal effects on the heart to be sino-auricular slowing or standstill and various grades of auriculoventricular block. Right carotid sinus pressure had a greater tendency to produce complete standstill. Left pressure had a greater tendency to produce complete auriculoventricular block. Ventricular escape from vagal inhibition, nodal rhythm and sinus arrhythmia occasionally occurred. P-wave changes were frequent and R-wave changes were less frequent. R-T segment and T-wave changes occurred comparatively rarely. It is suggested that the variations in response of the right and left nerves, as well as the difference in response in the different hearts, are dependent upon variations in the number of vagal terminals of the respective nerves in various portions of the heart.

I am indebted to Louis Gurian for his valuable assistance in the work connected with this paper.

REFERENCES

1. Rothberger and Winterberg: Über der Beziehungen der Herznerven zur Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* 135: 506, 1910.
2. Einthoven, W., and Wieringer, J. H.: Ungleichartige Vaguswirkungen auf das Herz Elektrokardiographisch Untersucht, *Arch. f. d. ges. Physiol.* 149: 48, 1913.
3. Cohn, A. E.: On the Differences in the Effects of Stimulation of the Two Vagus Nerves on Rate and Conduction of Dog's Heart, *J. Exper. Med.* 16: 732, 1912.
4. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw and Sons.
5. Robinson, G. C., and Draper, G.: Studies With the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart, *J. Exper. Med.* 14: 217, 1911.
6. Levine, S. A.: On Oculo-Cardiac Reflex, *Arch. Int. Med.* 15: 758, 1915.
7. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* 16: 1008, 1915.
8. Sigler, Louis H.: Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, *Am. J. M. Sc.* 175: 211, Feb., 1933.
9. Laslett, E. E.: The Relative Effects of Right and Left Vagus Nerves on the Human Heart, *Heart* 7: 347, 1918.
10. Kleeman, M.: Vagusdruck Versuch und Seine Bedeutung für die Herzfunktion, *Deutsches Arch. f. klin. Med.* 130: 221, 1919.
11. Ritchie, W. T.: Further Observations on Auricular Flutter, *Quart. J. Med.* VII: 1, 1913-14.
12. Sigler, Louis H.: Clinical Observations on the Carotid Sinus Reflex. I. The Frequency and the Degree of Response to Carotid Sinus Pressure Under Various Diseased States, *Am. J. M. Sc.* 186: 118, 1933.
13. Idem: Clinical Observations on the Carotid Sinus Reflex. II. The Response to Carotid Sinus Pressure at Various Ages and Heart Rates and Rhythms, *Am. J. M. Sc.* 186: 118, 1933.
14. Idem: Clinical Observations on the Carotid Sinus Reflex. III. The Response to Carotid Sinus Pressure in Cases With and Without Precordial Pain, *Am. J. M. Sc.* 186: 125, 1933.
15. Garey, Walter E.: The Effects of the Vagi Upon Heart Block and Ventricular Rate, *J. Physiol.* 30: 451, 1912.

THE ACTION OF QUININE AND QUINIDINE ON PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION*†

SIDNEY P. SCHWARTZ, M.D., AND ABRAHAM JEZER, M.D.
NEW YORK, N. Y.

THE purpose of this study was to determine the clinical manifestations and the successive changes in the rhythm of the heart following the intravenous administration of graded doses of quinine dihydrochloride and quinidine sulphate to patients with auriculoventricular dissociation subject to transient seizures of ventricular fibrillation. These drugs have been used both orally and intravenously with moderate success in the treatment and prevention of certain forms of the transient types of ventricular tachycardias.¹⁻⁵ Their administration in one form or another has been strongly advocated in the treatment and prevention of transient seizures of ventricular fibrillation on the ground that the frequency of such seizures would be greatly diminished by their use.⁶ Indeed, it has been suggested by Morawitz⁷ and others^{8, 9} that quinidine might be used with success as a prophylactic drug in patients regarded as liable to sudden death as a result of ventricular fibrillation.

The assumption that these drugs would be of therapeutic value in such patients seems to us to be based on very meager clinical experience, and in fact mostly on hypothesis. For while both quinine^{10, 11} and quinidine¹² have been demonstrated to have an inhibitory effect upon ventricular fibrillation produced in the experimental animal as a result of timed electrical stimuli, such transfers of practice are not applicable to human beings. On the contrary, it would appear from the very few clinical reports in the literature that quinidine may result in the development of transient ventricular fibrillation.

REVIEW OF LITERATURE

In 1921, Kerr and Bender¹³ reported observations on a male, sixty-eight years of age, who was observed over a year, during which time there were several attacks of cardiac syncope following the administration of quinidine sulphate. Electrocardiograms obtained during some of these attacks revealed transient ventricular fibrillation. They concluded that quinidine therapy was dangerous in such patients.

Unfortunately, some of their observations were made at a time when the ventricular rate varied between 40 and 70 beats per minute and when the ventricular rhythm was totally irregular. It is well established

*From the Medical Division of the Montefiore Hospital, Service of Dr. Leopold Lichtwitz.

†Aided by a grant from the Board of Trustees of Montefiore Hospital.

from our previous studies¹⁴ that when the basic ventricular rate in such patients behaves in this manner, syncopal attacks due to transient ventricular fibrillation may occur easily and spontaneously without the use of any drug.

Dock⁶ reported a male, aged thirty-six years, suffering from syncopal attacks that increased in frequency within one year. An electrocardiogram obtained at the end of one of these attacks revealed a ventricular arrhythmia with a rate of 285 beats per minute which, in his opinion, was ventricular fibrillation. He found that quinidine sulphate rationing prevented these attacks, although the patient still suffered from an occasional seizure during the following year. Although Dock's patient was apparently free from syncopal attacks due to transient ventricular fibrillation, it is very likely that if more electrocardiograms had been obtained in the year following his hospital admission, the basic rhythm would have revealed a pre-fibrillatory mechanism at some time or other during that period. In studying such patients one cannot rely solely upon the absence of syncopal attacks as a measure of the efficacy of a drug. Quinidine administered orally may produce a constant ventricular irregularity without ending in syncope, especially in the doses used by Dock. Without controls of the rhythm over long periods of time, it is difficult to evaluate the beneficial effects of the drug.

Davis and Sprague¹⁵ reported recurrent seizures of ventricular fibrillation in the course of quinidine therapy (123 grains in four days) in a woman whose basic rhythm prior to the use of the drug showed auricular fibrillation with bigeminal rhythm due to alternate premature ventricular beats. Again, in view of the fact that such a bigeminal rhythm may be the characteristic feature of the pre-fibrillatory mechanism in the spontaneous development of such seizures, it is unfair to incriminate the drug as responsible for these attacks. The ventricular fibrillation in their patient may have been a terminal phenomenon such as we have recently described in another patient.¹⁶

Finally, Escamilla¹⁷ observed a sixty-year-old male suffering from transient seizures of ventricular fibrillation to whom he administered quinidine at various intervals. Although he concluded that quinidine was of some value in his patient, he observed that the effect was not invariable enough to enable him to draw any absolute conclusions as to its efficacy. It is obvious from a review of the protocol of his case that adequate control studies of the ventricular rate and rhythm prior to or during the administration of quinidine are totally lacking. With these points in view, we attempted the following experiments.

METHOD OF STUDY

Two patients with auriculoventricular dissociation who were suffering from recurrent transient seizures of ventricular fibrillation form the subjects of this study. The natural course of the development of their

attacks and the successive changes in the rhythm of their hearts were studied by us carefully over a period of several years. During this entire time they were in the Montefiore Hospital, and hundreds of correlated observations were made on their heart rhythms at the same time that electrocardiograms were obtained.

These experiments were carried out at a time when it was certain that the patients had not had any transient seizures of ventricular fibrillation for at least twenty-four hours. It was definitely determined from constant study of both the heart rate and the pulse, with the patients attached in the electrocardiographic circuit, that the basic ventricular rate was fairly constant for at least four hours prior to the onset of an experiment. A basic ventricular rate that was almost regular and did not vary more than five beats per minute was considered an essential condition before initiating an experiment. When the basic rhythm was interrupted spontaneously by the appearance of premature ventricular beats, the number of such extrasystolic contractions was counted each minute for at least ten minutes prior to the use of any drug. The patients were kept in bed all the time, and no other medication was administered to them throughout the entire period of these studies. In one instance inhalations of amyl nitrite were given after quinidine had been used.

On several occasions and frequently before the drugs were used, the effects of the intravenous injection of 1 c.c. of either distilled water or physiological saline were determined in order to rule out any abnormal changes in the rhythm of the heart or in the complexes of the electrocardiograms that might follow the injection of the fluid itself.

One of us timed the clinical manifestations following the injection of the drugs, while the other recorded the time intervals at which changes appeared in the electrocardiograms. All studies were carried out with Lead II only. Successive changes in the rhythm of the heart were recorded as frequently as it was thought necessary, and observations of the movements of the galvanometer string were followed for several hours after the use of the drug unless the condition of the patient made it impossible to do so, in which case reliance was placed solely upon the clinical manifestations.

The minimal dose of the drugs that was necessary to produce transient changes in the rhythm of the heart was arrived at by the method of trial and error. Starting with very minute quantities, the dosage was gradually increased in repeated preliminary experiments until it was determined how much was needed to produce a pharmacological effect. The final amount used was based on the average amount required to give a specific effect.

Although innumerable observations were made from time to time, we have thought it advisable to describe only some of the typical protocols.

Each one of these demonstrates some mode of action of the drugs to which we direct particular attention. Since the effects on the heart rhythms have been somewhat variable each time, the sequence of the experiments has been rearranged so as to form a consecutive story. Before describing these alterations, however, it is important to call attention to the successive changes in the cardiac mechanism which take place when transient ventricular fibrillation develops spontaneously in patients with auriculoventricular dissociation so that comparisons can be made with such alterations in the rhythm of the heart which may be attributed to the influence of the drugs.

THE ALTERATIONS IN THE RHYTHM OF THE HEART PRECEDING TRANSIENT PERIODS OF VENTRICULAR FIBRILLATION

The alterations in the rhythm of the heart that precede transient periods of ventricular fibrillation during the presence of auriculoventricular dissociation are effected through (a) an increase in the basic idioventricular rate and (b) the interposition of premature ventricular beats either singly or in groups. These eventually lead to the development of short recurrent runs of aberrant ventricular oscillations which, in the final analysis, are short runs of ventricular fibrillation.

The basic idioventricular rate may at times be accelerated in the pre-fibrillatory period, and this acceleration may be brought about through a variety of mechanisms which have already been described elsewhere.^{18, 19} Obviously, the effects of any drug upon the cardiac mechanism in patients with auriculoventricular dissociation must first take into account the inherent variability of the idioventricular pacemaker in such patients at a time when they are free from symptoms due to transient ventricular fibrillation.

Prolonged observations on our two patients during their "quiescent" periods, when they are free from symptoms, revealed that there was a marked fixation of the inherent ventricular rate from day to day and at times from month to month. In both cases the average ventricular rate of from 27 to 31 beats per minute did not vary more than 5 beats per minute at the most at any one time. This relatively "fixed" ventricular rate was found to be the same during deep sleep as well as during undue exertion, excitement, or emotional disturbance. Respirations did not affect it and the use of adequate doses of atropine sulphate (gr. 1/120 intramuscularly) did not influence it, indicating that at such times the auriculoventricular pacemaker in them was not regulated by the extrinsic cardiac nervous mechanism. In both of these patients, when the increase in the basic ventricular rate appeared prior to the development of a transient seizure of ventricular fibrillation, the changes in the rate were gradual. Occasionally, such variations were easily appreciated by the patients, who complained of precordial distress. In

these periods of well-being, therefore, the idioventricular rates may be said, for practical purposes, to have been constant.

The changes in the rate of the idioventricular pacemaker in themselves are not sufficient to precipitate the type of ventricular fibrillation with which we are concerned. Sooner or later, either in the presence of a basically accelerated ventricular rate or frequently in its absence, premature ventricular beats begin to appear. These may at first alternate so as to produce a typical bigeminal rhythm, or they may increase in frequency before the interposition of aberrant ventricular oscillations begins to disrupt the rhythm. These ventricular oscillations can be appreciated clinically by the fact that only the first few beats associated with them are audible at the apical portion of the heart or palpable at the wrist. They are so frustrate in character that they are insufficient to open the aortic orifice, and consequently cerebral anemia sets in when they last for a period longer than from eight to ten seconds. If they last as long as forty seconds or more, a typical Stokes-Adams seizure occurs, with pallor of the skin and face, unconsciousness, stertorous breathing, incontinence of feces and of urine, a drop in blood pressure, and finally apnea, with intense cyanosis due to asphyxia. None of these phenomena has ever been seen to appear without the previous interruption of the basic idioventricular rhythm by recurrent short periods of ventricular oscillations which, in their final analysis, are short runs of ventricular fibrillation. Similar alterations in the cardiac mechanism have never been observed by us to follow the intravenous injection of either distilled water or physiological saline solution.

THE EFFECTS OF GRADED DOSES OF QUININE DIHYDROCHLORIDE IN PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION

Patients with transient seizures of ventricular fibrillation occurring during auriculoventricular dissociation vary in their response to the same dose of quinine dihydrochloride from time to time. The speed of injection does not influence this in any way when the same dose is used. The immediate result following the injection of quantities of up to $\frac{1}{2}$ c.c. of the solution ($1\frac{3}{4}$ grains of the drug) is usually a sensation of warmth which the patient feels all over the body. At times large beads of perspiration appear on the forehead, and the skin feels moist and clammy. Occasionally a sense of constriction is felt in the midsternal region, and with this there is a short period of restlessness that may be followed immediately by profound disturbances in the rhythm of the heart.

On one occasion, at a time when the basic ventricular rate averaged 31 beats per minute, the administration of $\frac{1}{2}$ c.c. ($1\frac{3}{4}$ gr.) of quinine dihydrochloride resulted in the appearance of only two premature ventricular beats nine minutes after the injection of the drug. However, when an additional dose of only $\frac{1}{4}$ c.c. ($\frac{7}{8}$ gr.) was injected forty-five

minutes after the first dose, there was an immediate but transitory increase in both the auricular and the ventricular rates from 100 and 31 beats per minute to 125 and 43 beats respectively. At the same time the ventricular complexes, which had previously been all of the upright form, now became variable in direction, assuming transitional changes from dextrograms to levograms.

One minute later there was a bigeminal rhythm due to premature beats of the ventricles. The auricular rate, however, was now lowered to 100 beats, and four minutes later there was a further reduction in the auricular rate to 83 beats per minute and in the ventricular rate to 26. Within five minutes, however, the rhythm assumed a bigeminy again, and exactly forty-five minutes after the injection of the second dose of the drug a transient period of ventricular fibrillation was ushered in by a pre-fibrillatory mechanism consisting at first of a bigeminal rhythm and then of a few short runs of aberrant ventricular oscillations before a typical Stokes-Adams seizure developed. There were repeated seizures of syncope after this that lasted for not more than one minute each before the rhythm returned to its original basic level of 31 beats per minute, about two and one-half hours after the beginning of the experiment.

On another occasion, after a control period during which the ventricular rate was fairly fixed and averaged 30 beats per minute, the injection of $\frac{1}{2}$ c.c. ($1\frac{3}{4}$ gr.) of quinine dihydrochloride resulted within six minutes in the development of a short pre-fibrillatory mechanism and one minute later in a typical Stokes-Adams seizure due to transient ventricular fibrillation. After recovery from this attack, the patient complained of palpitation of the heart due to irregular beating which, however, lasted only a few minutes before there was a return to the basic idioventricular rhythm with a regular rate of 32 beats per minute. This persisted for approximately one-half hour before another Stokes-Adams seizure appeared. This was ushered in by a few alternating premature beats of the ventricle with a very short run of grouped beats before the major attack developed. For the next hour these abnormal rhythms alternated with the basically regular rhythm until there was finally a restoration to the basic rhythm two hours after the injection of the drug.

A third observation in the presence of a fixed ventricular rate averaging 31 beats per minute was followed within three minutes after the injection of $\frac{1}{2}$ c.c. ($1\frac{3}{4}$ gr.) of the drug by a short run of ventricular fibrillation. There were two similar attacks five and seventeen minutes later, before these abnormal rhythms and their precursory mechanism disappeared altogether. Not until fifty minutes after the injection of the drug was the patient free from any irregularities of the heart. Then the basic rhythm with a ventricular rate of 31 beats per minute returned and remained regular after that.

In another observation, at a time when alternate premature beats of the ventricle constantly interrupted the basic auriculoventricular dissociated rhythm, the injection of variable doses of the drug ranging from $\frac{1}{4}$ to $\frac{1}{2}$ c.c. resulted within a few minutes in the development of short runs of multiple premature ventricular beats or in the appearance of the pre-fibrillatory mechanism which disappeared, however, within from one-half to one hour after the injection.

In the light of these experiences no attempt was made to try the drug during an actual period of ventricular fibrillation.

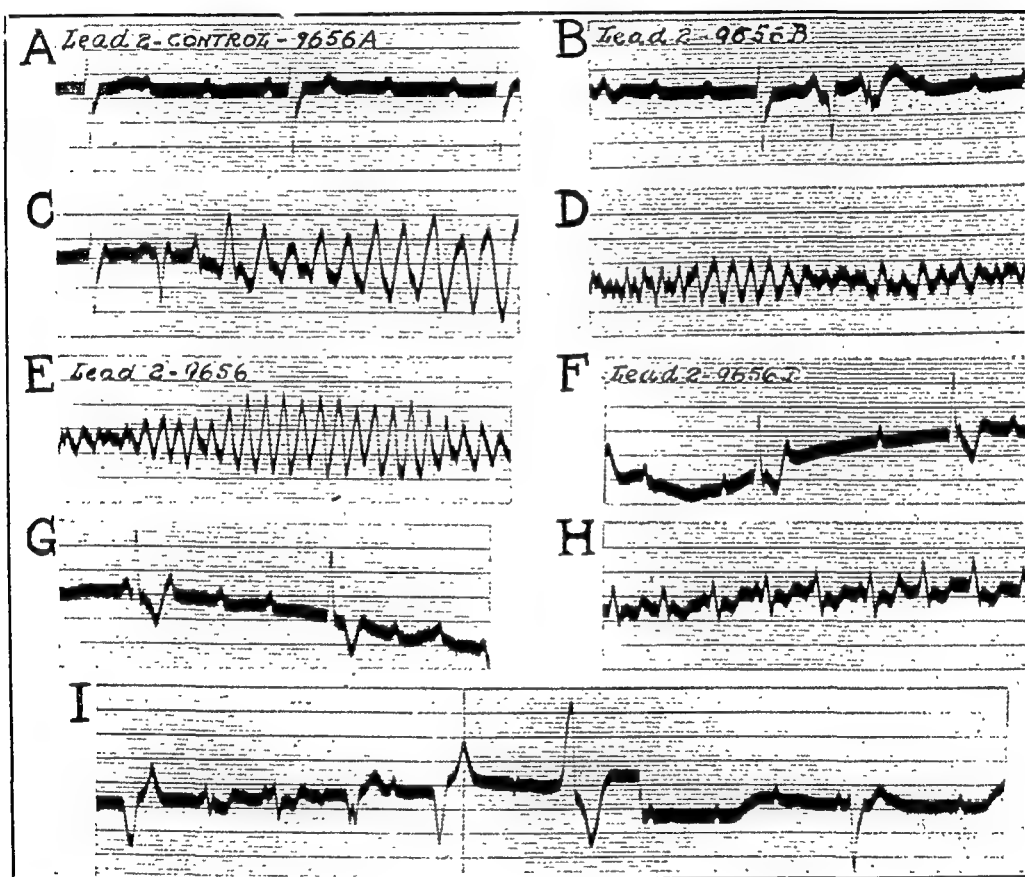


Fig. 1.

Fig. 1.—Portions of continuous strips (Lead II) showing the development of a transient seizure of ventricular fibrillation following immediately the intravenous injection of $\frac{1}{8}$ of a grain of quinidine sulphate.

A, Control, the basic ventricular rhythm; B, the pre-fibrillatory mechanism; C, the mechanism initiating ventricular fibrillation; D and E, records obtained during a Stokes-Adams seizure; F and G, the intermediary idioventricular rhythm following ventricular fibrillation; H, the post-fibrillatory tachysystole; I, the gradual restoration to the basic rhythm.

THE EFFECTS OF GRADED DOSES OF QUINIDINE SULPHATE ON PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION

The intravenous injections of 1 c.c. ($\frac{1}{6}$ gr.) of quinidine sulphate to a patient whose ventricular rate averaged 28 beats per minute and who showed only one premature beat of the ventricles during a control period in which the rate was counted every minute for one and one-

half hours, resulted in the immediate appearance of multiple premature ventricular beats. These premature beats persisted either singly or in groups for the next forty-five minutes, when they gradually disappeared and the basic rhythm returned to normal. On the further injection of $1\frac{1}{2}$ c.c. of the drug ($\frac{1}{4}$ gr.) one-half hour after the first dose, there developed immediately multiple premature beats. Within two minutes there was a short pre-fibrillatory mechanism, and for the next twenty-five minutes there was a constant and fixed bigeminal rhythm due to

TABLE I

CHARACTERISTIC PROTOCOL SHOWING THE SUCCESSIVE CLINICAL AND GRAPHIC MANIFESTATIONS FOLLOWING THE ADMINISTRATION OF ONE-THIRD OF A GRAIN OF QUINIDINE SULPHATE. SEPTEMBER 15, 1933, PROTOCOL NO. 2B

TIME	VENTRICULAR RATE	DRUG USED	RHYTHM	COMMENT	EKG. NO.
2:35 P.M.	31	Quinidine sulphate (2 c.c. $\frac{1}{4}$ gr.) intravenously	Regular.	Comfortable. No complaints.	9656-A
2:40 P.M.	29				
2:43 P.M.	30				
2:45 P.M.	31				
2:48 P.M.	31				
2:53 P.M.	33				
2:58 P.M.					9656-B
3:00-3:01 P.M.					
3:01 P.M.			Pre-fibrillatory process and ventricular fibrillation.	Typical Stokes-Adams seizure.	9656-B
3:02 P.M.			Ventricular fibrillation.	Typical Stokes-Adams seizure.	9656-C
3:03 P.M.			Post-fibrillatory period	Unconscious.	9656-D, E
3:03-3:04 P.M.				Unconscious.	9656-F
3:05 P.M.				Screams. Complaints of palpitation.	9657-A
3:06 P.M.				Dyspneic.	9658
3:07 P.M.			Recurrent periods of pre-fibrillatory process.		9659
3:08 P.M.					9660
3:10 P.M.					9661
3:11 P.M.				Pulse small, hardly perceptible, gradually increasing in intensity with the return of the regularity of the rhythm.	9662
3:12 P.M.					
3:14 P.M.	32		Regular.		9663
3:19 P.M.	32		Regular.		
3:20 P.M.				Comfortable.	9663
3:25 P.M.	33				
3:30 P.M.	33			Comfortable.	

alternate premature beats of the ventricles. All abnormalities of the cardiac mechanism disappeared one-half hour after the second injection.

On another occasion (Table I, Protocol No. 2B) the use of 2 c.c. of the drug ($\frac{1}{3}$ gr.) resulted in the immediate development of a Stokes-Adams seizure due to a period of ventricular fibrillation (Ekg. No. 9656-B) that lasted for over one and one-half minutes.

These examples will suffice to point out the rapidity with which the effects of quinidine sulphate appear in contradistinction to those following quinine dihydrochloride.

These observations reveal then that both quinine and quinidine administered intravenously in relatively small doses to patients suffering from transient seizures of ventricular fibrillation result in the development of irregularities of the heart that lead to syncopal attacks, all due to ventricular fibrillation. There is no need to assume that the oral administration of these drugs can likewise lead to similar irregularities instead of abolishing them as has been thought by some. It takes much longer for these drugs to be absorbed by the oral route and to show their effects on the cardiac mechanism. Such studies are at present in progress and will be reported later.

The action of both quinine and quinidine on the ventricles being as complex as it is, no attempt is made at present to offer any explanation for the manner in which these drugs initiate the irregularities leading up to transient ventricular fibrillation.

SUMMARY AND CONCLUSIONS

1. Quinine dihydrochloride and quinidine sulphate were administered intravenously in graded doses to two patients with auriculoventricular dissociation who were subject to transient seizures of ventricular fibrillation.

2. The drugs were injected at a time (a) when the basic idioventricular rate did not vary more than five beats per minute over a period of several hours prior to their use, and (b) when premature ventricular beats interrupted the basic rhythm. The number of these was counted for each minute during the hour preceding the injections. The tests were carried out at a time when it was definitely known that the patients had been free from syncopal seizures for at least twenty-four hours prior to the injections of the drug.

3. It was determined that such patients with transient seizures of ventricular fibrillation responded variably to the same dose of both quinine dihydrochloride and quinidine sulphate at different times.

4. The intravenous administration of small doses of quinine dihydrochloride (maximum dose: $1\frac{3}{4}$ grains) and quinidine sulphate (maximum dose: $\frac{1}{3}$ grain) resulted in the development of either a pre-fibrillatory mechanism or transient periods of ventricular fibrillation within from one to nine minutes after the injection.

5. Once the pre-fibrillatory mechanism is precipitated by the administration of the drug, recurrent periods of transient ventricular fibrillation may follow for several hours at a time.

6. The intravenous injection of these drugs resulted in a more rapid appearance of ventricular fibrillation when premature ventricular beats were already present prior to the onset of the experiment.

7. Since the intravenous use of these drugs precipitated transient periods of ventricular fibrillation in patients who are subject to such seizures, the use of such drugs by this method is contraindicated in such patients.

REFERENCES

1. Hecht, A. F., and Zweig, W.: Ueber einen Fall von ventrikularen Extrasystolie und paroxysmaler Anfallen von Kammerautomatie und deren therapeutische Beeinflussung, *Wien. klin. Wchnschr.* 30: 167, 1917.
2. Winterberg, H.: Die Herzwirkung des Chinins bei Störung der Reizleitung und Reizbildung, *Wien. klin. Wchnschr.* 33: 459, 1920.
3. Singer, R., and Winterberg, H.: Chinin als Herz und Gefäßmittel, *Wien. Arch. f. inn. Med.* 3: 329, 1922.
4. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation, *Arch. Int. Med.* 49: 808, 1932.
5. Boden, E.: Ueber Tachycardie und ihre Behandlung, *Klin. Wchnschr.* 6: 1564, 1927.
6. Dock, W.: Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, *AM. HEART J.* 4: 709, 1929.
7. Morawitz, P., and Hochrein, M.: Zur Verhütung des akuten Herztodes, München. med. Wchnschr. 76: 1075, 1929.
8. Stepp, W., and Parade, G. W.: Untersuchungen und Betrachtungen über den plötzlichen Herztod durch Kammer-Flimmern, München. med. Wchnschr. 75: 1869, 1928.
9. Weber, A.: Ueber den plötzlichen Herztod, *Klin. Wchnschr.* 6: 2458, 1927.
10. Hoffman, F. B.: Die Wirkung einiger organischer Salze und des Chinins auf die Tätigkeit des Säugetierherzens, *Ztschr. f. Biol.* 66: 293, 1916.
11. Hecht, A. F., and Rothberger, C. J.: Experimentelle Beiträge zur Kenntnis der Chininwirkung bei Herzflimmern, *Ztschr. f. d. ges. exper. Med.* 7: 134, 1919.
12. Levine, H. D.: Effect of Quinidine Sulphate in Inhibiting Ventricular Fibrillation, *Arch. Int. Med.* 49: 808, 1932.
13. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulphate Therapy, *Heart* 9: 269, 1921.
14. Schwartz, S. P.: Transient Ventricular Fibrillation. A Study of the Electrocardiograms Obtained From a Patient With Auriculo-Ventricular Dissociation and Recurrent Syncopal Attacks, *Arch. Int. Med.* 49: 282, 1932.
15. Davis, D., and Sprague, H. B.: Ventricular Fibrillation. Its Relation to Heart Block, *AM. HEART J.* 4: 559, 1929.
16. Schwartz, S. P., and Jezer, A.: Studies on Transient Ventricular Fibrillation. I. Observations on the Alterations in the Rhythm of the Heart Preceding Syncopal Seizures in a Patient With Normal Sinus Rhythm, *Am. J. M. Sc.* 4: 187, 1934.
17. Escamilla, R. F.: Report of a Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, *AM. HEART J.* 8: 850, 1933.
18. Schwartz, S. P., and Jezer, A.: Transient Ventricular Fibrillation. The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient With Auriculoventricular Dissociation, *Arch. Int. Med.* 50: 450, 1932.
19. Schwartz, S. P., and Jezer, A.: The Stokes-Adams Syndrome. Some Clinical and Graphic Observations on the Cardiac Mechanism Underlying Syncopal Seizures. *M. Clin. North America* 17: 213, 1933.

VENOUS PRESSURE IN THYROID DYSFUNCTION*

J. S. GOLDEN, M.D., AND WILLIAM A. BRAMS, M.D.
CHICAGO, ILL.

SIGNIFICANT variations in venous pressure have been described in congestive heart failure, ascites, arterial hypertension, local obstruction to venous return, certain endocrine disturbances, pregnancy, and various experimental conditions. There are comparatively few reports on venous pressure in thyroid dysfunction, and the recorded observations which are available are meager and contradictory. L. Payan, E. Giraud, and M. Assada² injected thyroid extract intramuscularly and noted variable changes in venous pressure. A temporary fall was usually observed when signs of thyrotoxicosis were well developed. M. Villaret, F. Saint Girons and L. Justin-Besancon³ note briefly that they usually found an elevation of venous pressure in a few cases of Basedow's syndrome. V. Jonas¹ studied 43 patients with hyperthyroidism and found an elevation in venous pressure in 26 (60 per cent), in some of whom the pressure returned to normal when the thyroid symptoms were improved. Some of these patients showed variable degrees of cardiac failure. There appeared to be no correlation between the height of arterial and venous pressures in this series.

PRESENT STUDY

Our material consisted of thirteen patients with definite evidence of Basedow's syndrome and two with myxedema. None of the Basedow patients showed evidence of cardiovascular embarrassment, and only one of the myxedema patients (M. W.) complained of dyspnea on exertion. Basal metabolic rates, pulse rates, systolic and diastolic pressures and venous pressures were determined in all patients. Blood pressure was estimated by the auscultatory method with the patient in the supine position; a mercury sphygmomanometer was employed. Venous pressure was determined by the direct method using a hollow needle inserted into the median basilic vein and connected with a suitable water manometer. The entire system was filled with a sterile 3 per cent sodium citrate solution in order to hinder clotting. The solution was permitted to run into the vein in small amounts at frequent intervals in order to test the patency of the needle. The usual precautions of keeping the patients under basal conditions in estimating venous pressures were observed. The final reading was made

*From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

when the fluid in the manometer was stabilized and the height of the column was practically the same after at least three attempts were made at intervals of a few minutes. A summary of the results obtained may be seen in Table I.

TABLE I

PATIENT	BASAL METABOLIC RATE	BLOOD PRESSURE IN MM. OF MERCURY	PULSE	VENOUS PRESSURE IN MM. OF 3 PER CENT SODIUM CITRATE SOLUTION
<i>Basedow's Syndrome</i>				
F. Y.	plus 52%	148/ 90	96	64
M. O.	plus 40%	124/ 50	112	80
C. W.	plus 63%	180/120	108	90
E. O.	plus 45%	154/ 76	108	82
M. B.	plus 56%	172/ 78	120	77
M. K.	plus 27%	120/ 88	92	90
G. W.	plus 31%	130/ 62	108	72
C. K.	plus 32%	138/ 84	116	70
J. B.	plus 23%	155/ 75	128	55
S. L.	plus 48%	120/ 80	104	102
H. S.	plus 30%	124/ 78	108	69
A. S.	plus 62%	160/ 90	116	50
F. D.	plus 38%	140/ 90	100	67
<i>Myxedema</i>				
M. W.	minus 34%	140/ 90	64	95
G. H.	minus 48%	110/ 80	44	52

Five of the patients with Basedow's syndrome were subsequently subjected to subtotal thyroidectomy, and similar studies were made after the basal metabolic rates became stabilized at a normal level. Both myxedema patients were given sufficient thyroid extract to elevate the basal metabolic rate, in one of them to a normal level, in order to

TABLE II

PATIENT	BASAL METABOLIC RATE		BLOOD PRESSURE IN MM. OF MERCURY	PULSE	VENOUS PRESSURE IN MM. OF 3 PER CENT SODIUM CITRATE SOLUTION
<i>Basedow's Syndrome Before and After Thyroidectomy</i>					
F. Y.	Before operation—	plus 52%	148/ 90	96	64
	After operation—	plus 2%	150/120	92	75
M. O.	Before operation—	plus 40%	124/ 50	112	80
	After operation—	plus 10%	114/ 66	112	65
C. W.	Before operation—	plus 63%	180/120	108	90
	After operation—	plus 7%	168/110	78	75
E. O.	Before operation—	plus 45%	154/ 76	108	82
	After operation—	minus 10%	152/104	72	85
M. B.	Before operation—	plus 56%	172/ 78	120	77
	After operation—	minus 10%		108	98
<i>Myxedema Before and After Administration of Thyroid Extract</i>					
M. W.	Before thyroid—	34%	140/ 90	64	96
	After thyroid—	1%	136/ 94	80	80
G. H.	Before thyroid—	48%	110/ 80	44	52
	After thyroid—	26%	110/ 76	72	72

study the effect of elevating the metabolic rate on venous pressure. The results of reducing and elevating the basal metabolic rate on venous pressure, pulse rate, and arterial pressure are summarized in Table II.

RESULTS

In contrast to the previously quoted reports, our studies failed to reveal any significant deviations from the normal in venous pressure either in the thirteen cases of Basedow's syndrome with elevated basal metabolism or in the two patients with myxedema. Our results are within the usually accepted upper and lower limits of normal venous pressure. The five patients with Basedow's syndrome who were subsequently subjected to subtotal thyroidectomy showed a return to normal variations in basal metabolism after operation, the fall in metabolic rate varying from 30 to 66 per cent and yet in none of these patients was there a significant change in venous pressure from the level before operation. The slight changes which were found were well within the limits of experimental error and were inconstant in direction. The same lack of change was true in the cases of the two patients with myxedema, in one of whom the basal metabolic rate was elevated from -34 to -1 per cent and in the other, from -48 to -26 per cent by administration of thyroid extract.

It is peculiarly significant that even in the same patient no noteworthy changes in venous pressure occurred after such marked differences in basal metabolism as were produced by thyroidectomy in Basedow patients or by administration of thyroid extract in myxedema. It was also significant that no apparent relation existed between changes in pulse rate or blood pressure and venous pressure during such large variations in basal metabolism.

It is evident that in this series of patients neither an elevation nor a depression of basal metabolic rate was sufficient to cause significant changes in venous pressure. This was true whether the rise or fall in basal metabolic rate was due to disease or to therapeutic procedures. These results do not exclude the possibility that venous pressure may be altered by changes in basal metabolic rate under certain experimental conditions. One may conclude, however, that the degree of change occurring under the conditions in this study was not of sufficient magnitude to be reflected in the form of significant variations in venous pressure even though the changes in basal metabolic rate were striking.

SUMMARY

1. Venous pressure was found to be normal in a series of thirteen patients with Basedow's syndrome and an elevated basal metabolism,

and in two patients with myxedema and a subnormal metabolic rate. None of the fifteen patients presented evidence of cardiac embarrassment.

2. These findings are in contrast with those previously reported in the literature. It is possible that cardiac failure or variations in experimental technic affected the results previously reported.

3. This study is of significance because no definite change in venous pressure occurred in the *same* patient when the basal metabolic rate was markedly reduced by thyroidectomy in those with Basedow's syndrome or by an elevation in metabolic rate by administration of thyroid extract in myxedema.

4. The degree of change in metabolism, pulse rate and blood pressure was apparently of insufficient magnitude in this series of patients to be reflected as important variations in venous pressure.

We are indebted to Dr. S. G. Taylor of the Medical Department of the Cook County Hospital for the patients used in this study.

REFERENCES

1. Jonas, V.: Časop. lék. česk. 70: 1217, 1931.
2. Payan, L., Giraud, E., and Assada, M.: Compt. rend. Soc. de biol. 95: 490, 1926.
3. Villaret, M., Saint Girons, F., and Justin-Besancon, L.: La Pression Veineuse Peripherique, p. 267, Paris, 1930, Masson et Cie.

Department of Clinical Reports

LONG CONTINUED VENTRICULAR TACHYCARDIA

REPORT OF AN UNUSUAL CASE*

ARTHUR R. ELLIOTT, M.D., AND GEORGE KARL FENN, M.D.
CHICAGO, ILL.

ISOLATED premature ventricular contractions form, with the exception of sinus arrhythmia, the most common irregularity of the heart beat recorded graphically. Paroxysms, or runs of ventricular premature beats constituting ventricular tachycardia, are on the contrary of rare occurrence. The first case with electrocardiographic studies was reported by Lewis¹ in 1909. Strauss² in 1930 in a painstaking review of the subject collected 63 cases possessing what he considered adequate diagnostic criteria. To these he added two cases of his own, bringing the total to 65 properly attested cases. Roger Froment³ devotes a monograph of 501 pages to this subject. Although tracings are not reproduced in all instances, it seems likely that 66 of his 99 collected cases would meet the requirements strictly necessary for proper identification. Froment's work and that of Strauss are in close agreement. Strauss' study of the age incidence disclosed the fact that 26 per cent of the cases occurred in individuals of over sixty years, 60 per cent between fifty and sixty years, and 14 per cent before fifty years of age. Three cases only were recorded in individuals under the age of thirty years. Paroxysmal ventricular tachycardia has usually been observed to occur in association with some established cardiac disease. In a very much smaller percentage of recorded cases it has appeared to be spontaneous—without laboratory or clinical evidence to throw light on its etiology. Among Strauss' 65 collected cases 11 were of this type. The condition is sufficiently uncommon to warrant the reporting of isolated instances, especially if they be of this cryptic type.

This report deals with the clinical and electrocardiographic studies of a patient who developed, at the age of nineteen years, paroxysms of ventricular tachycardia which persisted with increasing frequency and growing duration until her eventual death, approximately nine months after their first appearance. We were able to observe five separate paroxysms varying in duration from thirty-seven hours to thirty-two days. The case is of interest because of the youth of the patient, the

*From Medical Service A. St. Luke's Hospital, Chicago.

absence of all other signs of heart disease, and the unprecedented duration of the paroxysms.

CASE REPORT

Hospital No. 275,953. American-born Hebrew girl, aged nineteen years, was admitted to St. Luke's Hospital July 7, 1931, complaining of shortness of breath and attacks of palpitation of the heart of six months' duration; nausea and vomiting were often associated with these paroxysms. There had been some edema of the feet for one week. The patient had but very recently been graduated from one of our state universities, where she had proved herself to be a remarkable student, having made Phi Beta Kappa in three years. Previous to going to college she had always been well. Her mother affirmed that the girl had never had a serious illness, in particular denying the occurrence of chorea, arthritis, heart disease, or other significant infection. Patient's tonsils had been removed at the age of ten years. She was very obese. Her body weight at time of hospital entry was 225 pounds. At the age of seventeen years and during her sophomore year at college, having become extremely sensitive over her obesity, she joined a research diet squad, living on rations which approximated 1,000 calories daily. She remained on this regimen for four months, losing seventy pounds in body weight. Her physical efficiency suffered considerably as a consequence of this rapid reduction, and she was compelled to return to more liberal fare. During her senior year in college, her body weight at the time being considerably over 200 pounds, she returned to a strict reduction diet as nearly duplicating her earlier efforts in that direction as she could, her declared object being to reduce her weight to 150 pounds before graduation. She presently began to experience shortness of breath and periods of rapid heart action, sometimes with nausea and vomiting. This was about Christmas, 1930. For a number of weeks at the outset these manifestations were infrequent and transient, subsiding spontaneously. As spring approached, they became more frequent, severe, and prolonged; and she sought medical advice. The medication first administered was digitalis. This failed either to prevent or to shorten the attacks appreciably, and during April her physician administered quinidine.

This proved more effective, ameliorating the severity of her symptoms sufficiently to enable her to continue her college work until graduation. Shortly thereafter (May, 1931) she experienced an unusually severe attack and was admitted to the Michael Reese Hospital, where she remained ten days. Upon discharge from hospital observation her medication consisted of quinidine, rest in bed, and ice bag to precordium. Despite faithful adherence to this regime, attacks of palpitation continued to occur, averaging in duration from seven to ten days. The heart rate during attacks varied from 180 to 210. At times she vomited and was always extremely restless and unable to sleep. A particularly severe and prolonged attack of rapid heart action led to the development of swelling of her feet, and it was alarm over this manifestation that brought her to the hospital July 7. The patient's mother stated that during the month of June there had been administered 72 grains of digitalis besides more or less (unestimated) quinidine. Since the beginning of the attack the pulse had varied around 200.

Physical examination July 7, 1931. The patient was seen to be an unusually large and very obese girl, orthopneic and cyanotic. The heart rate was regular, 184 per minute counted with the stethoscope. No murmurs could be detected. The soft tissues of the feet and legs were the seat of pitting edema. The liver was enlarged two fingerbreadths and was somewhat tender to pressure. There seemed

to be a good deal of moisture at both lung bases. Signs of free fluid in thoracic and abdominal cavities were lacking. Great difficulty was encountered in properly adjusting the blood pressure cuff to the patient's fat arm. She complained greatly of the pressure from inflation of the cuff and resisted the procedure in a childish manner, so that no satisfactory blood pressure reading was ever secured. The urine analysis was reported as practically negative. The blood count was: red cells 4,860,000; leucocytes 12,500; hemoglobin 97 per cent or 21.83 gm. per 100 c.c. The blood chemistry proved practically normal. After ten days' incubation, blood culture was reported sterile. The two-meter x-ray film revealed a slight amount of fluid in the right thoracic cavity and a moderate increase in the transverse measurement of the heart.

Subsequent History.—To relieve her difficult breathing and mediate the cyanosis, oxygen was administered with much apparent benefit. The patient complained bitterly of pain in the neck which we interpreted as perhaps due to the constant forceful pounding of the great vessels of the neck. On the fourth day the heart rate suddenly slipped to 88, with a regular rhythm, the heart sounds being weak and indistinct. Her sensory discomforts quickly subsided, and there was some improvement in the edema. This remission which began on July 11 continued until 4:30 P.M. July 15 when the rate suddenly went to 200, with nausea and vomiting. This recurrence of the tachycardia was preceded by an emotional upheaval due to a disturbing family conference. After forty-eight hours of tachycardia the rate slowed to 120 with occasional premature contractions. On the following day the pulse was very irregular, heart rate 96, radial pulse 76. Free fluid was now demonstrable in the abdomen. There had developed a trophic ulcer over the sacrum. The body temperature varied from subnormal to 100° F. After forty-eight hours of moderate rate the heart action suddenly became again extremely rapid, with frequent skips. This paroxysm, during which the heart rate varied from 170 to 210, continued without observed intermission for eighteen days. During this exhausting paroxysm the edema greatly increased and fluid accumulated considerably in abdomen and right pleural sac. Acid base diuretics with salyrgan proved ineffectual in influencing this anasarca. Drainage of the legs with Southey's tubes was attempted but could not be continued owing to the objection of the patient. The liver became greatly enlarged and tender. All efforts at therapeutic control proved ineffectual. Quinidine by mouth and intravenously exerted no apparent influence. After eighteen days' continuous tachycardia the heart rate declined to 120 and subsequently to 92. An electrocardiogram made during this remission showed a rate of 102, sinus rhythm. This period of normal control continued for four days, and on occasion during this interval the heart was observed to be grossly irregular for short periods. After this brief improvement ventricular tachycardia again began and continued without observed interruption until death, a total of thirty-two days. Multiple decubital ulcers developed. Large hemorrhagic blisters which began as purpuric areas formed on the lower extremities. The patient died in terminal coma apparently from exhaustion. Consent for necropsy could not be secured.

During the period of our observation there occurred five paroxysms of ventricular tachycardia. The attacks persisted for four days; thirty-seven hours; eighteen days; four days; and thirty-two days, making in all a total of fifty-nine and one-half days.

ELECTROCARDIOGRAPHIC STUDIES AND DISCUSSION

Four tracings are presented, in at least two of which the diagnosis of paroxysmal ventricular tachycardia appears to be clearly established. A third tracing showing normal sinus rhythm during interparoxysmal

intervals is also presented. A fourth record is added differing in some details from all preceding ones, difficult to interpret beyond argument. An exactly similar tracing has never before been observed in our laboratory, nor does a fairly comprehensive search of available literature reveal one with identical characteristics.

Fig. 1 is a tracing made July 9, thirty-six hours after patient was admitted to the service. It shows paroxysmal ventricular tachycardia with complete dissociation, ventricular rate being 174 while auricular rate was 90. P-waves are upright in all leads; auricular cycle length 0.66; QRS notched and extremely aberrant; QRS cycle length 0.38; T_1 almost isoelectric; T_2 and T_3 cannot be identified.

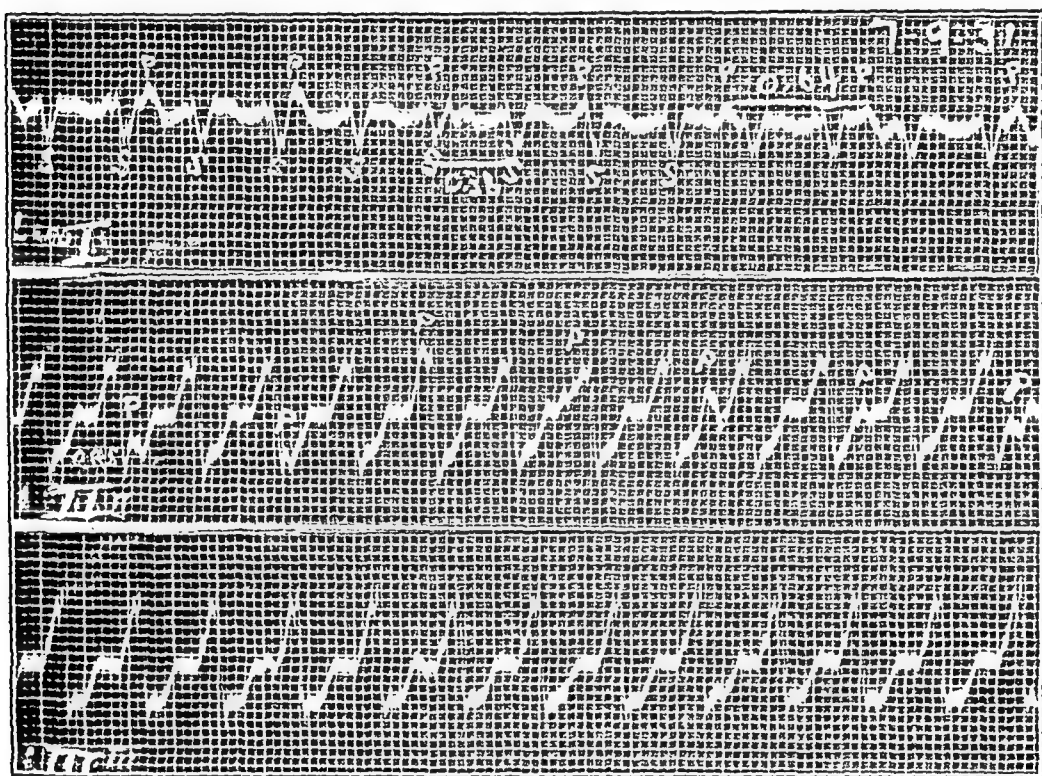


Fig. 1.

Fig. 2 is a record made July 31, three weeks after the tracing in Fig. 1, and during this interval normal sinus rhythm had prevailed for seventeen days. It is identical in all particulars with preceding curve except that QRS complex is upright in Lead I.

Fig. 3, August 5. Normal sinus rhythm. Heart rate 102. P-wave upright in Leads I and II with notching in Lead II. P-wave almost isoelectric in Lead III, T_1 and T_2 depressed. QRS complex shows low amplitude in all leads together with notching and slurring. One ectopic contraction of ventricular origin occurs in Lead III.

The final identification of the character of a paroxysm of tachycardia may be said to rest absolutely with the electrocardiogram. This is often

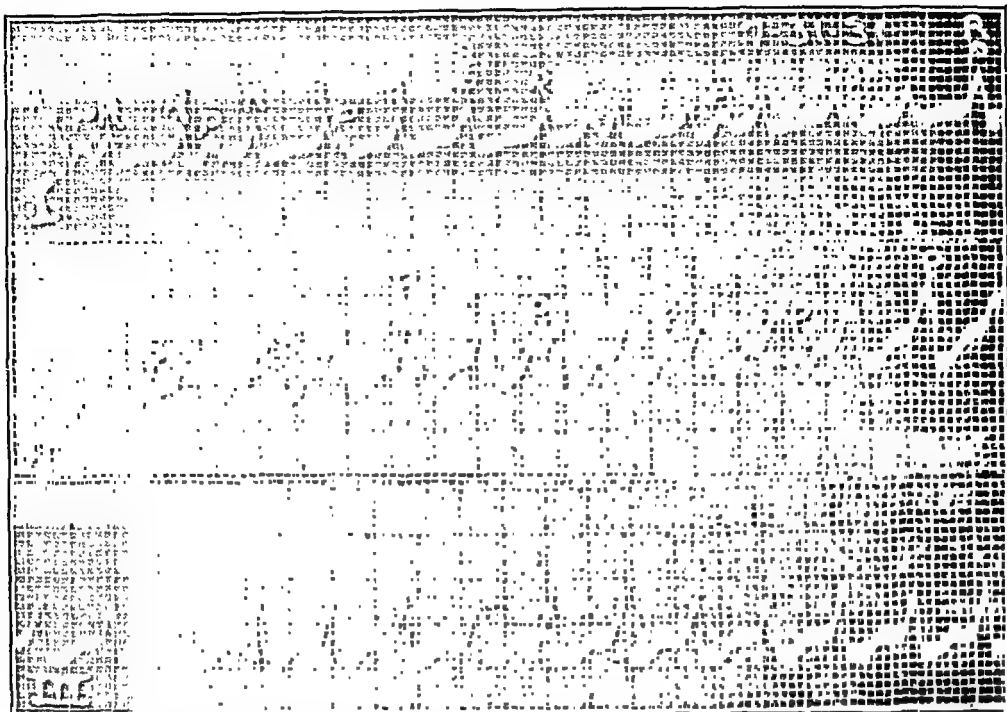


Fig. 2.

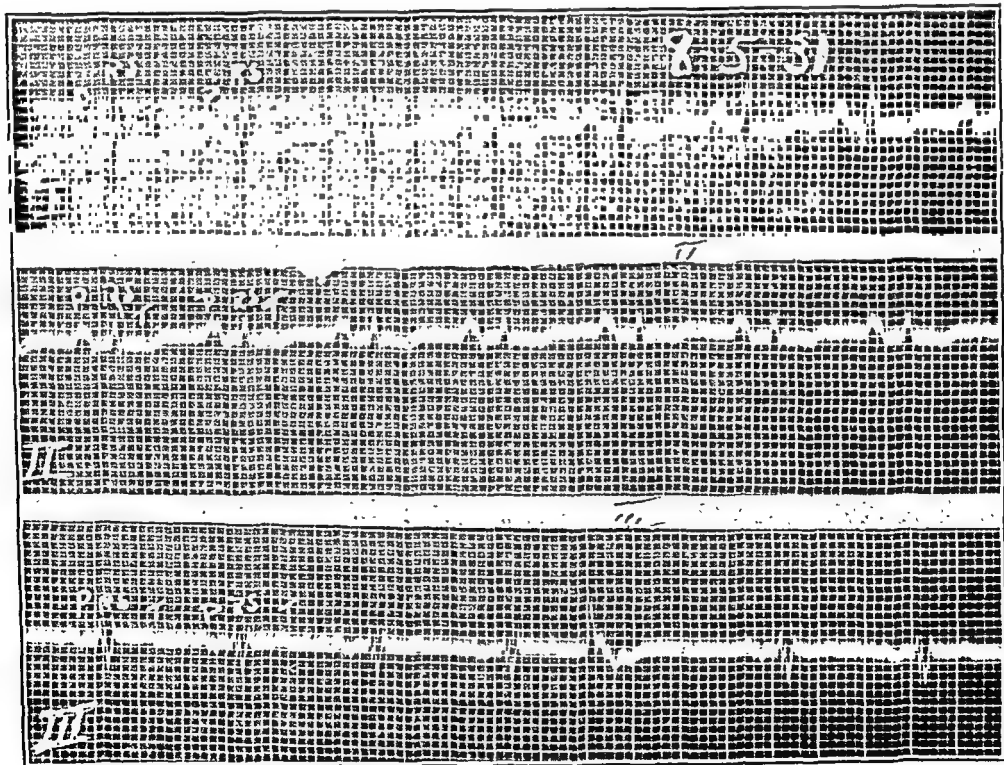


Fig. 3.

attended by considerable difficulty owing to variations and restrictions that have nullified many instances that were placed on record as ventricular tachycardia. If accuracy be observed in enforcing certain

criteria now generally recognized and acknowledged⁴ paroxysmal ventricular tachycardia becomes a disorder that is rarely encountered.

Reference to the electrocardiograms here presented will admit no doubt of the diagnosis in tracings 1 and 2.

Fig. 4, August 19. This tracing presents a different problem. While the diagnosis of paroxysmal ventricular tachycardia seems fairly obvious, the mechanism is quite different from that exhibited in the preceding

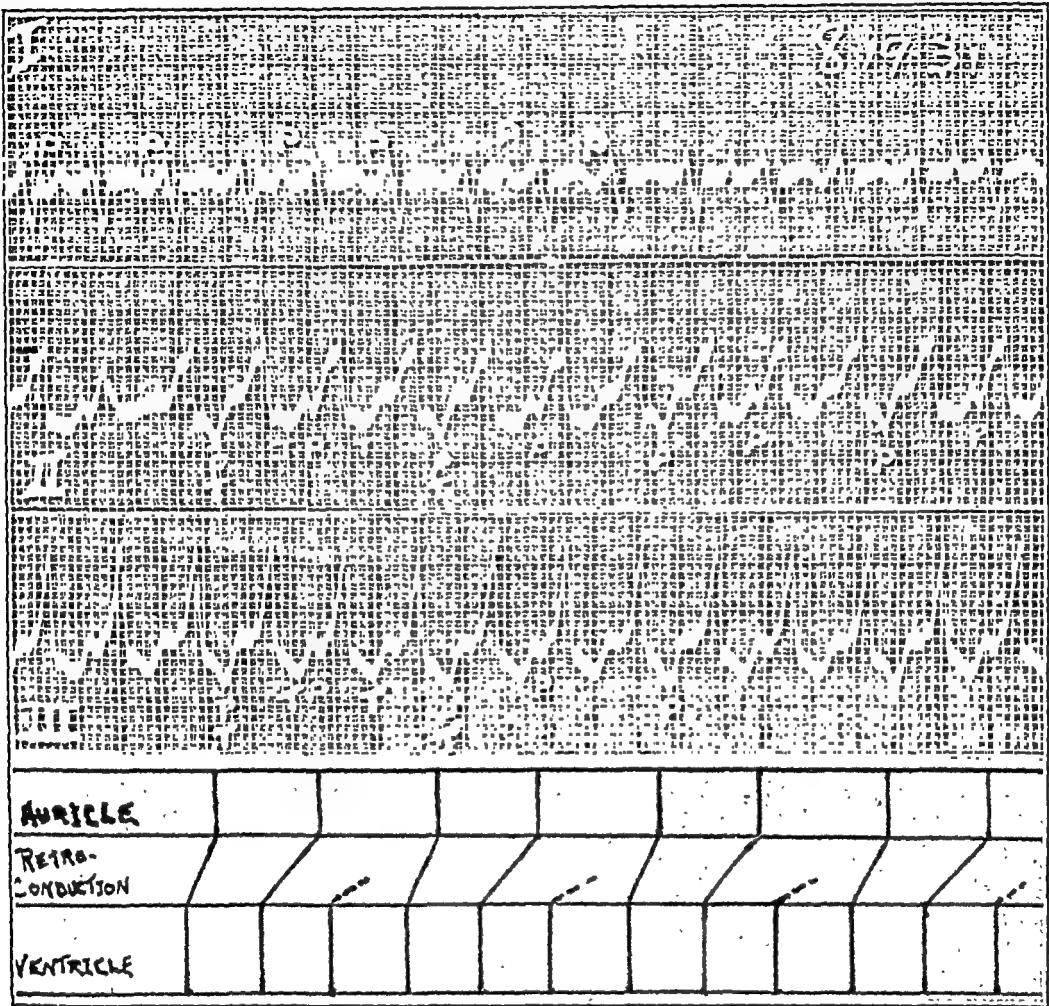


Fig. 4.

tracings. Two alternative interpretations are offered, neither one of which is entirely satisfactory.

1. Paroxysmal ventricular tachycardia with retrograde conduction and ventriculo-auricular block. This interpretation assumes that the pacemaker of the heart lies in the ventricle, and the auricle is activated by impulses travelling upward from the ventricle. The rhythm consists of a series of triads in which the first ventricular impulse provokes a prompt auricular response; the second ventricular impulse provokes a delayed auricular response; and the third ventricular impulse fails entirely to activate the auricle. This is the reverse of the Wenckebach type

of A-V block. Such an interpretation might well explain the events occurring in Leads II and III, but in Lead I it would assume that the first retrograde P-wave of each triad is upright, while the second is inverted. This assumption is not entirely satisfactory. If the first triad of Lead I be closely examined, it will be seen that both P-waves are inverted. It is this interpretation that has been illustrated in the tracing shown above.

2. Somewhat less satisfactory is the interpretation that tracing 4 represents paroxysmal ventricular tachycardia with complete dissociation between auricles and ventricles and a bigeminal auricular mechanism with alternate auricular impulses arising from different sources. Such a reading might be borne out by the auricular complexes themselves, but it presupposes a time relationship between the dissociated auricle and ventricle that could be brought about only by a very strange and perhaps unlikely coincidence.

SUMMARY

There is reported herewith an inveterate and fatal instance of paroxysmal ventricular tachycardia occurring in a girl of nineteen years without any other discoverable evidence of cardiac disease. The paroxysms were of unprecedented duration. The terminal paroxysm ending in death from cardiac exhaustion endured continuously for thirty-two days.

REFERENCES

1. Lewis: *Lancet* 1: 384, 1909.
2. Strauss: *Am. J. M. Sc.* 179: 337, 1930.
3. Froment, Roger: *Les Tachycardies Paroxystiques Ventriculaires*, Paris, 1932, Masson et Cie.
4. Robinson and Herrman: *Heart* 8: 59, 1921

ACUTE DIFFUSE MYOCARDITIS FOLLOWING EXFOLIATIVE DERMATITIS

ROBERT LYMAN NELSON, M.D.
DULUTH, MINN.

REFERENCES to acute diffuse myocarditis have appeared in medical literature since 1896. Various authors have utilized the terms acute interstitial myocarditis, acute myocarditis, acute isolated myocarditis, and Fiedler's myocarditis. The clinical pictures presented in the various reports vary too widely to consider it a clinical entity. The terminology must, therefore, depend on the pathologist.

In 1929 Scott and Saphir¹ found 36 reported cases in the literature and added two more. In 1931 Bailey and Andersen,² in adding one more, dispute the inclusion of three of the cases. This is mentioned to establish the relative rarity of the condition. A review of the above works will readily justify the inclusion of this case. In no instance has exfoliative dermatitis been listed as an etiological factor.

CASE REPORT

A. F., a Norwegian laborer, aged forty-two years, was admitted to St. Mary's Hospital on the Dermatology Service of Dr. George Doyle on August 13, 1931. The patient complained of malaise and itching all over the body. The skin of the entire body was red and edematous. It was a generalized dermatitis in the pre-exfoliative stage.

A search into the man's past brought out the following history of syphilis. About twenty years before he had had an initial lesion. A small but undetermined amount of treatment was given at that time. In September, 1930, a routine employment examination brought to light a strongly positive blood Wassermann reaction. At this time he received one bismuth and one neoarsphenamine injection. He was not seen again until July, 1931, when in seeking employment his record again brought him under treatment. He sought no symptom relief and complained of no illness. He was given three injections of bismuth and five neoarsphenamine injections of 0.3 gm. each. The first four injections were without untoward effect, but on the day following the fifth injection the skin itched and became red. This continued to increase in intensity, and two days later he was admitted for hospital care. Five injections of sodium thiosulphate and local treatment failed to check the advance in severity.

On August 24, eleven days after admission, he became dyspneic, the heart tones were weak, and the pulse was difficult to palpate. He improved under the use of stimulants and the oxygen tent.

On August 25 the skin was more edematous, and the crusting exudate of the exfoliative process was more pronounced. He was bringing up a frothy purulent material on coughing. Coarse moist râles were noted in the right upper lung field, and there was diminished resonance below. Temperature was 99° and respirations were 36.

On August 26 I made my first examination. He was lying flat in bed and appeared very ill. The skin of the entire body was covered by a scaly crust. Breathing was too labored to justify much questioning. He complained of feeling very sick, of an intolerable itching all over the body (which necessitated bandaging to keep him from scratching), and of difficulty in getting enough air. On physical examination the left lung seemed practically clear, but the right lung showed an extensive congestion with no demonstrable consolidation. A flat film of the chest taken in bed showed the above plus a questionable small area of bronchopneumonia in the left base. The heart outline was of the hypertensive type. Diathermy was applied to the chest, the oxygen tent was used and 10 c.c. of solution of digitalis were given intramuscularly during the course of the day.

On August 28 the patient felt better. The skin was unchanged, and the cough

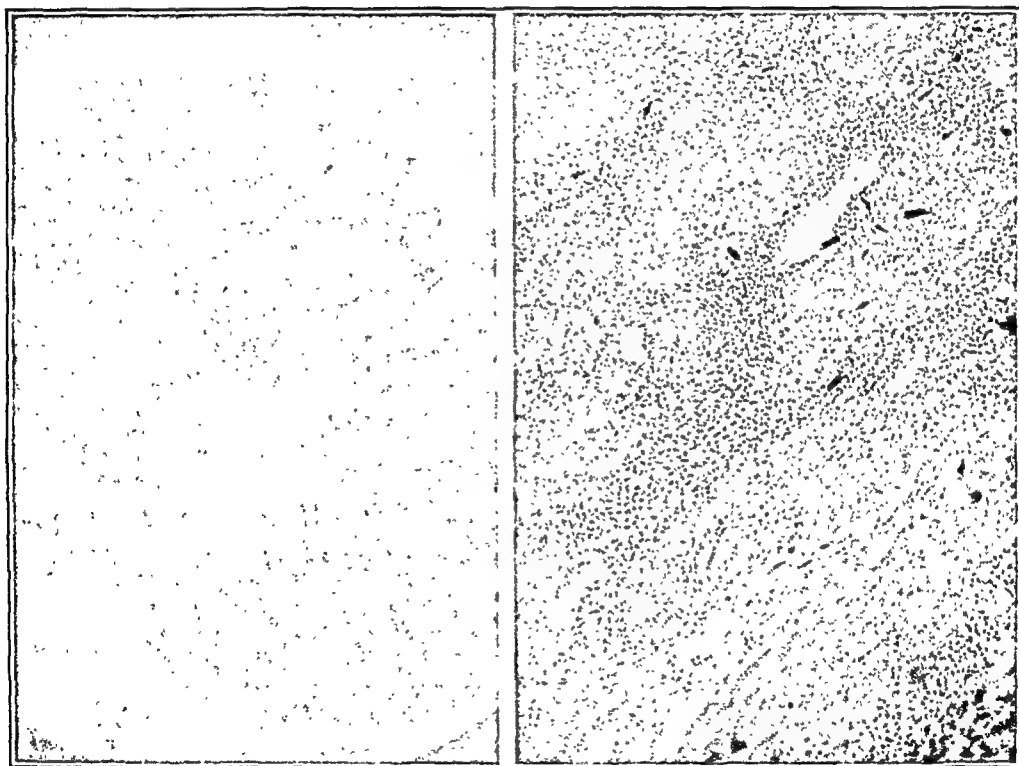


Fig. 1.—Low power.

Fig. 2.—High power.

was easier and productive of a thick sputum. Six c.c. of digitalis were administered intramuscularly.

On August 30 the patient was weaker. The lungs were clearer, and coarse moist râles were heard over both bases. (It must be remembered that the dermatitis made auscultation difficult.) No consolidation was clinically demonstrable.

On August 31 the patient died suddenly. Owing to delay in locating relatives for purposes of securing permission, the autopsy was performed on the embalmed body under unfavorable conditions. The following positive findings were taken from the notes of the pathologist, Dr. G. L. Berdez.

The skin was red, desquamated and scaly with a serous exudate and a general edema. Multiple hemorrhagic infarcts were present in both lungs. There were 200 c.c. of fluid in the left pleural cavity and 150 c.c. in the right. The spleen was congested and there was cloudy swelling of both kidneys.

The heart weighed 720 grams and showed a diffuse myocarditis. There were no mural thrombi. There were some yellowish atheromatous plaques in the aorta, not extending into the coronary orifices or onto the aortic valves. The lumen of the coronary arteries showed not more than a Grade I narrowing at any point along the main branches. Cut sections showed a yellowish muscle of rather flabby consistency with grayish yellow mottling. The accompanying photomicrographs show a diffuse interstitial infiltration, mostly with lymphocytic and other mononucleated cells (Fig. 1). In Fig. 2 in the higher magnification, in addition to the above, polymorphonuclear cells are also numerous. There is a moderate amount of cloudy swelling and actual destruction of muscle fibers. No bacteria are noted.

DISCUSSION

In the recorded cases the most frequent clinical notations are sub-sternal pain or oppression, congestive heart failure and sudden death. What chest pain this man had was ascribed to the rapidly appearing pulmonary congestion and the possible bronchopneumonia. The congestive heart failure was rather acute in onset eleven days after admission. Sudden death might have occurred at that time if emergency measures had not been available.

The commonest description of the heart muscle is that of grayish yellow mottled streaks on a background of dark red muscles of flabby consistency. This varies from plain dark red to streaked yellow and sometimes grayish red. This case showed the yellowish color of cloudy swelling.

The heart weighed 720 grams. This is higher than any figure given in previous reports. The flat plate of the lungs showed what was interpreted as a hypertensive outline. We are without benefit of blood pressure readings due largely to the severe dermatitis. At the age of forty-two years it is improbable that a great degree of long standing hypertension could account for much of this. No aortic insufficiency was noted. It therefore is reasonable to suppose that the bulk of the cardiomegaly, at least, was due to inflammatory changes in the myocardium.

Four main possible causes must be weighed: first, the syphilis itself; second, the direct action of the arsenic; third, the bronchopneumonia; and fourth, the exfoliative dermatitis with its associated infection or toxemia.

Since Warthin's original work,³ much has been said regarding acute myocardial failure occurring in cases of latent syphilitic myocarditis. In these cases demonstration of the *Spirocheta pallida* has usually been possible in isolated areas, though diffuse cases have been reported. In the many sections studied in this case no spirochetes were demonstrated.

The direct action of the arsenic is certainly open to conjecture. Obviously there was a low tolerance or idiosyncrasy to the drug. It does seem, however, that a direct reaction would have occurred more rapidly in the form of cardiac embarrassment. It is presumed that the

direct action is in the nature of a dramatic allergic phenomenon and that as such it would more nearly approximate the chronological onset of the skin manifestations.

The autopsy findings ruled out a direct infection from bronchopneumonia, for what was thought to be bronchopneumonia turned out to be an area of infarction.

Lastly comes the question of the exfoliative dermatitis. The literature and the experience of those men who were kind enough to discuss this case offer no precedent. The expedient of exclusion leaves the dermatitis as the most probable cause of the myocarditis. The absence of bacteria suggests the toxic rather than the infectious nature.

SUMMARY

1. A case is reported in which a pathological diagnosis of acute diffuse myocarditis was made.

2. A brief comparison with the most constant findings in other cases is made.

3. Exfoliative dermatitis is believed to be the direct cause.

A case is reported of late, latent syphilis in which treatment by arsenic was followed by exfoliative dermatitis. During this attack severe cardiac symptoms appeared and progressed rapidly to a fatal issue. The lesions of acute diffuse myocarditis were found at autopsy.

The exfoliative dermatitis is believed to have been the cause of the myocardial changes.

REFERENCES

1. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, *AM. HEART J.* 5: 129, 1929.
2. Bailey, F. R., and Andersen, Dorothy H.: Acute Interstitial Myocarditis, *AM. HEART J.* 6: 338, 1931.
3. Warthin, A. S.: Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis, *AM. HEART J.* 1: 1, 1925.

Department of Reviews and Abstracts

Selected Abstracts

Waring, James J., and Black, W. C.: The Syndrome of Obstruction in the Lesser Circulation. *Am. J. M. Sc.* 187: 652, 1934.

This survey of the symptoms of obstruction in the lesser circulation has been undertaken to emphasize the too frequently forgotten importance of the integrity of the pulmonary circulation in the process of oxygenization.

The clinical evidences of chronic anoxemia are commonly dyspnea, cyanosis, and polycythemia, rarely precordial pain and syncope. Signs of slowly developing strain upon the right side of the heart in the absence of other obvious cause, such as valvular defects, suggest obstruction in the lesser circulation. Whether the obstruction be in the capillaries, as in certain instances of so-called Ayerza's disease, or in the arterioles and small arteries or whether the obstruction be in the larger divisions of the pulmonary arteries, the underlying clinical picture of chronic anoxemia and failure of the right side of the heart is essentially the same.

Primarily obstructive lesions of the pulmonary circulation which involve extensively the pulmonary capillaries or pulmonary arteries and are not immediately fatal raise the pulmonary arterial pressure and produce hypertrophy of the right ventricle and also interfere with respiratory function and produce anoxemia.

Horton, Bayard T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography. *Am. J. M. Sc.* 187: 649, 1934.

This case report serves to illustrate the importance of definitely determining the site of an arteriovenous fistula by means of arteriography and to demonstrate the clinical signs and symptoms of acquired arteriovenous fistula. With the history, the presence of a bruit, the thrill over the right thigh and the bradycardiac reaction, the diagnosis of arteriovenous fistula of the acquired type seemed definitely established. The diagnosis was confirmed by the demonstration of a high admixture of arterial and venous blood in the right femoral vein. The site of the fistula could be determined only by means of arteriography or by surgical exploration.

Griffith, George C., Chamberlain, Charles T., and Kitchell, J. Roderick: Observation on the Practical Significance of Venous Pressure in Health and Disease With a Review of the Literature. *Am. J. M. Sc.* 187: 642, 1934.

In this article the authors discuss the clinical application of determinations of venous pressure and the usefulness of the procedure in the hands of the general practitioner who is confronted with diagnostic problems of cardiovascular disease. There is a brief discussion of the normal venous pressure and its physiologic variations. Four fundamental functional factors affecting peripheral

venous pressure namely: (1) vis a tergo or heart action; (2) intrathoracic pressure; (3) hydrostatic level; (4) volume of blood in the vein are discussed.

Use of venous pressure determinations in various clinical conditions is discussed. It is pointed out in particular that in primary congestive heart failure and in other disease entities complicated by or simulating cardiac decompensation, the procedure should offer practical diagnostic, prognostic, and therapeutic aid. The significance of venous hypotension is discussed.

Goldbloom, A. Allen: Clinical Evaluation of Lead IV (Chest Leads). *Am. J. M. Sc.* 187: 489, 1934.

The purpose of this study was to see whether Lead IV would be positive only in those cases where the routine three leads were positive or whether it might sometimes be positive while the routine three leads were negative. If the fourth lead were positive only in conjunction with positive routine three leads, it would be superfluous as an additional method; but, if it should prove positive in any case where the routine three leads were negative or doubtful, it would be of definite value. All the 86 patients were ambulatory except 13. Forty of the 86 patients had definite clinical symptoms of coronary artery disease with or without a history of acute occlusion. The method carried out in this series was that of Wolferth and Wood; although in a few cases posteroanterior position was also used and proved of value.

Of these cases with coronary artery disease, 28 showed positive routine 3 leads, 12 showed an abnormality in Lead IV and positive routine 3 leads, and 3 showed an abnormality only in Lead IV. Four of the 13 cases of acute coronary thrombosis showed an abnormal Lead IV, whereas the routine 3 leads were negative.

A serial study of a case of coronary thrombosis showed that abnormal Lead IV may persist long after abnormal changes have disappeared from routine 3 leads. Since abnormal Lead IV proves positive in cases of coronary artery disease and acute coronary thrombosis, its employment as a routine electrocardiographic method is advocated.

Schwartz, Sidney P., and Jezer, Abraham: Studies on Transient Ventricular Fibrillation. I. Observations on the Alterations in the Rhythm of the Heart Preceding Syncopal Seizures in a Patient With Normal Sinus Rhythm. *Am. J. M. Sc.* 187: 469, 1934.

Clinical manifestations were correlated with electrocardiograms of the alterations in the rhythm of the heart of a boy with infectious myelitis during a period when he was experiencing recurrent syncopal attacks, each of several minutes' duration. Prior to such seizures, there was at first an acceleration of the basic sinus rate from an average of 90 to 150 beats per minute but the rhythm was regular. Sooner or later, in an unpredictable manner, premature ventricular beats began to disrupt the basic rhythm, first appearing after every fourth normal beat and then alternately after every other normal beat. To these premature beats there were added from time to time recurrent groups of aberrant ventricular oscillations, only the first two or three which could be heard at the apical region of the heart or felt at the pulse, thus resulting in periodic irregular "pulse pauses." When the duration of these "pulse pauses" was only eight or ten seconds, there was momentary loss of consciousness with pallor of the skin. If they lasted between twenty and forty seconds, there was loss of consciousness. If they were of a duration longer than forty seconds, there resulted a typical Stokes-Adams seizure with loss of consciousness, epileptiform convulsions, incon-

tinence of feces and urine and stertorous breathing ending in apnea with intense cyanosis.

These recurrent periods of aberrant ventricular oscillations are short runs of ventricular fibrillation, and their presence in the electrocardiographic tracings was the most characteristic feature of the alterations in the rhythm of the heart that preceded syncopal seizures in this patient.

Schwartz, Sidney P., and Hauswirth, Louis: *Studies on Transient Ventricular Fibrillation. II. Observations on the Alterations in the Rhythm of the Heart Preceding Syncopal Seizures in a Woman With Transient Auriculoventricular Dissociation.* Am. J. M. Sc. 187: 478, 1934.

Successive electrocardiograms were correlated with the clinical manifestations of a woman who was suffering from recurrent syncopal seizures. Particular attention was paid to the alterations in the rhythm of the heart that preceded syncope.

The patient usually showed normal sinus rhythm in between attacks. For some time prior to a seizure, the normal sinus rhythm alternated with that of auriculoventricular dissociation. There was a marked waxing and waning of the rates of both the auricles and the ventricles during the presence of auriculoventricular dissociation.

Sooner or later this dissociated rhythm would be interrupted by premature ventricular beats coming on singly so as to form a bigeminal rhythm. Occasionally a normal sinus beat would be interpolated in this dissociated rhythm, appearing at first after every eighth effectual ventricular contraction and then more frequently. Alterations between the normal sinus rhythm and the dissociated rhythm resulted in grouped beats forming trigeminies and quadrigeminies with regular periodicity.

When the appearance of these various rhythms had materially increased the rate of the ventricles after they had been slowed during auriculoventricular dissociation, recurrent ventricular oscillations began further to disrupt the cardiac mechanism. These aberrant ventricular oscillations were variable in shape, size, and form from beat to beat. They were associated clinically with ineffectual ventricular contractions resulting in periodic "pulse pauses," absent heart sounds, and a collapse of the circulation.

If these ventricular oscillations lasted from eight to ten seconds, then the patient merely shut her eyes, and her face assumed an ashen gray pallor. If they were of twenty seconds' duration, she lost consciousness. If they lasted longer than forty seconds, a typical Stokes-Adams seizure ensued.

These short groups of ventricular oscillations are short runs of ventricular fibrillation, and no syncopal seizure resulting from ventricular fibrillation appeared without these shorter runs heralding a major attack. Because of this, they are pathognomonic for ventricular fibrillation, and their recurrent presence in any electrocardiogram should help in the diagnosis of the cardiac mechanism underlying such syncopal seizures.

Seecof, David P., Linegar, Charles R., and Myers, Victor C.: *The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles.* Arch. Int. Med. 53: 561, 574.

Studies have been made on the creatine content of the right and left ventricular muscle on 114 human and 9 animal hearts. The method employed for the creatine determination is a modification of that of Rose, Helmer and Chanutin. It was found that the concentrations of creatine of the left and right ventricular muscles of the heart are different, the former having the greater concentration.

Attention has also been called to correlations between creatine content and age and weight of the heart. From the standpoint of creatine and creatinine metabolism, it is significant that when the creatine content of voluntary muscle exceeds about 400 mg. (the probable saturation point) a corresponding elevation in the cardiac muscle also occurs, and further, that the retention of creatinine in renal disease has an augmenting influence on the creatine content of both cardiac and voluntary muscle.

In addition to embryological, anatomical, physiological and pathological observations, chemical evidence is now presented pointing to the fact that the left and right ventricles are different muscles. These differences justify the concept that the heart is not a uniform muscle but that it is made up of several qualitatively different muscles. The significance and possible practical value of this concept are discussed.

Harrison, W. G., Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure. XVIII. Clinical Types of Nocturnal Dyspnea. *Arch. Int. Med.* 53: 561, 1934.

A clinical study has been made of thirty patients who had cardiac disease and who suffered from attacks of nocturnal dyspnea. Most of the subjects were more than forty years of age. The chief causes of cardiac disease in these cases were hypertension, arteriosclerosis, and syphilitic aortic insufficiency. There were only two patients with rheumatic heart disease, and of these only one had uncomplicated mitral stenosis. The occurrence of nocturnal dyspnea is restricted almost entirely to patients with disorders which cause a strain on the left ventricle. Uncomplicated syphilitic aortitis (i.e., without aortic insufficiency, occlusion of the coronary vessels or aneurysm) practically never causes nocturnal dyspnea.

Cardiac enlargement and diminished vital capacity were constant objective findings; premature beats and gallop rhythm occurred in a large number of the patients. Only four patients in the series had auricular fibrillation.

The following factors have been found to be precipitating and predisposing causes of the attacks: (1) the position of the body in twenty-seven cases, (2) cough in twenty-three cases, (3) the amount of activity engaged in during the preceding day in twenty-one cases, (4) abdominal distention in seventeen cases, (5) large evening meals in twelve cases, (6) constipation and desire for bowel movement in twelve cases, (7) hunger in eight cases, (8) unpleasant dreams in eight cases, (9) heat in eight cases, and (10) urination in seven cases.

Analysis of the histories of the cases indicates that nocturnal dyspnea may be subdivided into several types of respiratory distress:

1. A type which is not paroxysmal but which develops gradually during the course of the day, usually appearing first in the late afternoon and reaching its maximum intensity at bedtime. For this syndrome the name "evening dyspnea" is proposed.

2. Attacks of shortness of breath appearing only at the onset of sleep and tending to prevent the patient from reaching a state of deep sleep. However, if such a patient falls into a sound sleep, he is likely to remain free from attacks throughout the remainder of the night. Patients with this type of dyspnea frequently exhibit Cheyne-Stokes respiration and are unlikely to have seizures of acute pulmonary edema.

3. Attacks of dyspnea which begin after the patient has begun to sleep soundly and which are likely to cause acute edema of the lungs. Cheyne-Stokes respiration is an infrequent finding in patients with this type of dyspnea.

4. Combination forms. The same patient may have all three types of dyspnea or any two of them.

In subsequent articles objective observations will be presented concerning these various forms of respiratory distress.

Parker, Frederic, Jr., Keefer, Chester S., Myers, Walter K., and Irwin, Ralph L.: Histologic Changes in the Knee Joint With Advancing Age. *Arch. Path.* 17: 516, 1934.

Histological examination of the tissues from 100 knee joints of patients who had died of miscellaneous diseases was made. The gross anatomical changes have been reported in a previous article. The examination revealed the following observations: The synovia was essentially normal except in cases in which there were alterations in the cartilage. In these the capsule was somewhat thickened, papillary projections of the synovia occurred, and occasionally there were small collections of lymphocytes about the blood vessels. The cartilage showed fibrillation, degeneration, and some areas of regeneration. In some cases it was completely destroyed.

The subchondral bone was thickened owing either to compression or to formation of new bone. The marrow spaces were frequently filled with fibrous tissue, cysts, and areas of cartilage. Bony projections or so-called exostoses were due to a projection of bone and cartilage over the edge of the joint surface or to a depression of the cartilage below its original level, thus giving the appearance of bony overgrowth. They resulted from a forcing outward of bone and cartilage by flattening of the joint surface owing to pressure and erosion.

These changes are identical with those previously described as characteristic of degenerative arthritis. The evidence is that they are the result of injury and repair and that they occur with increasing frequency with advancing age.

Gilchrist, A. Rae: Ephedrine Sulphate and Barium Chloride in the Prevention of Stokes-Adams Seizures. *Brit. M. J.* 1: 610, 1934.

In six cases of complete heart-block ephedrine taken orally increased the rate of ventricular beating in four. In two patients the test was indecisive. Barium chloride produced no demonstrable effect on the ventricular rate in the four cases responding to ephedrine. It did no harm in doses larger than those originally recommended.

In two cases of complete heart-block complicated by occasional Stokes-Adams seizures, ephedrine taken for two and one-half and one and one-half years respectively proved entirely successful in the prevention of syncopal attacks. When the drug was discontinued, typical seizures returned.

It is recommended that the dose of ephedrine should be the minimum quantity consistent with an acceleration of the resting ventricular rate. Larger doses may cause overstimulation. If the drug be then suddenly omitted, profound slowing of the ventricular rate, with repeated Stokes-Adams attacks may occur as a result, presumably of exhaustion of the idioventricular center. A dose of one-half grain by mouth at eight-hour intervals may be sufficient. In the absence of positive findings, it is difficult to credit barium chloride with the power of preventing Stokes-Adams seizures.

Perry, C. Bruce: The Peripheral Circulation in Acute Lobar Pneumonia. *Quart. J. Med.* 3: 273, 1934.

In an attempt to provide definite evidence that the condition in pneumonia called heart failure is usually the direct sequel of failure at the periphery of the circulation rather than in the heart, a study of the failure of the small vessels

of the skin in patients with lobar pneumonia has been made. The reactions of the small vessels of the skin were studied in 26 cases of lobar pneumonia. Observations were made on the skin color, the blood pressure, the response of the skin vessels to histamine, to stroking and to adrenalin, and finally the back pressure on the circulation required to accelerate the blanching produced by the latter.

These reactions show an impaired efficiency in the contractility of the capillaries at the height of the disease. The recovery of the capillaries is slow and not immediately affected by the crisis. Part at least of the circulatory failure met with in lobar pneumonia is due to this impaired efficiency of the small blood vessels. The blood pressure is raised rather than lowered during the acute phase of the disease.

Bain, C. W. Curtis: Observations in the Speed of the Circulation. *Quart. J. Med.* 3: 237, 1934.

The time taken for the blood to travel from the arm to the face in normal subjects as shown by the histamine flush test is twenty-two seconds. The normal range is from nineteen to twenty-five seconds. The flush times are fast in hyperthyroidism, in the effort syndrome, in advanced anemia, and in diseases of the lung.

In the diseases of the heart some patients have had normal flush times; they have not been incommoded by their hearts. Others who have had no symptoms have had flush times from twenty-five to thirty seconds. These may be regarded as having a measure of cardiac insufficiency. Dyspnea and effort angina appear when the flush times have slowed to thirty-one seconds. It is suggested that dyspnea and effort angina should be regarded as alternative symptoms of cardiac failure.

Venous congestion is found in about half of those whose flush times are thirty-two seconds or more. The remainder include those suffering from anginal attacks and those who have been prevented from overexerting themselves. Edema is an almost constant finding in those whose flush times are forty-two seconds or more.

The above figures apply only when the lungs, blood, and basal metabolism are normal. When heart failure is complicated by pulmonary diseases, advanced anemia, or hyperthyroidism, the flush times are faster. Corresponding to the grade of failure, the heart will be less severely damaged than would be the case if these complications were absent, and great improvement may be expected if they can be removed.

Hirsch, I. Seth: The Recording of Cardiac Movements and Sounds by the Roentgen Ray (Kymophonoroentgenography). *Radiology* 22: 403, 1934.

The author describes a simple graphic method of obtaining a permanent record of the movements of the heart on a single film. Essentially this method is roentgenography through a slit diaphragm placed close to the object in motion, the recording film not being at rest as in ordinary roentgenography but moving at a constant rate of speed at right angles to the direction of the slit. The apparatus is of the multiple slit type. It consists of an impervious plate with slits of equal width, a mechanism for moving a film at a constant speed behind a grid, a mechanism for energizing the x-ray tube shortly after this movement begins and for cutting off the energization of the tube shortly before the film movement ends.

It is believed that this kymographic method contributes the following information to the morphological and physiological study of the heart: (1) the actual make-up of the cardiac shadow; (2) the shape of the heart as a whole, or any

of its chambers during the various phases of movement; (3) size of the heart in systole and diastole or any intermediate phase; (4) characteristics of the movement of the heart as a whole or of its various chambers; (5) activity and accomplishment of the cardiac muscle; (6) the relationship of contraction to conduction phenomena; and (7) the relationship of movement to sound phenomena.

Ayman, David: Heredity in Arteriolar Hypertension. Arch. Int. Med. 53: 792, 1934.

To determine more clearly the presence of a familial or hereditary factor in arteriolar (essential) hypertension, a direct study of the blood pressure, height, and weight of 1,524 members of 277 families was made.

It was found that in 780 members, aged from fourteen to thirty-nine years, of the second generation of the families, elevated systolic and diastolic blood pressure readings (140 systolic and 80 diastolic, or higher) occurred in 148 subjects. These 148 subjects had the same average age and sex incidence as the entire group of 780 children, but they were 14.3 pounds above the average weight compared to 4.5 pounds above the average weight for the normal children.

The families studied were then grouped according to the presence or absence of arteriolar (essential) hypertension in one or both parents. In the families whose parents had absolutely normal blood pressures, the incidence of elevated blood pressures in the children was only 3.1 per cent. In the families in which one parent had arteriolar hypertension, the incidence of elevated readings in the children rose to 28.3 per cent. In the families in which both parents had arteriolar hypertension the incidence of elevated readings in the children reached the striking level of 45.5 per cent.

Of 70 brothers and sisters of parents with normal blood pressures, 37.3 per cent had elevated blood pressure readings; whereas of 86 brothers and sisters with arteriolar hypertension, 65.3 per cent had elevated blood pressure readings.

Finally, 18 families, in which parts of three generations were available, were studied and results were found strikingly similar to those given in the preceding paragraph.

The results presented show that there is an unusually high incidence of elevated blood pressure readings in the children, brothers, sisters, and parents of subjects with arteriolar hypertension, as compared with similar relatives of subjects with normal blood pressure. These results are strong evidence for the existence of a hereditary factor in arteriolar (essential) hypertension.

Harrison, William Groce: Cerebrospinal Fluid Pressure and Venous Pressure in Cardiac Failure. Arch. Int. Med. 53: 782, 1934.

The cerebrospinal fluid pressure is markedly elevated in persons with congestive heart failure.

The cerebrospinal fluid pressure, except for slight variations, usually runs closely parallel to the venous pressure in the prone position in persons with cardiac failure; and, as a rule, the average ratio between the spinal fluid pressure and the venous pressure (1.6) in the patient with cardiac disease corresponds closely to that in the normal person. In general, either may be predicted from knowing the other.

The fall in cerebrospinal fluid pressure usually runs closely parallel with the fall in venous pressure as the patient with cardiac failure regains compensation.

Spinal drainage in patients with congestive heart failure was followed by a fall in venous pressure in eight instances, by a rise in two instances, and by no change in three instances. In the majority of cases spinal drainage was followed by a decrease in dyspnea.

The cisternal pressure is much less in patients in the sitting than in the prone position, although the systemic venous pressure and spinal fluid pressure are greater. This difference in cisternal pressure and hence in cerebral venous pressure is more pronounced in patients with cardiac failure; its bearing on orthopnea is discussed.

The relationship of the increased intracranial pressure to Cheyne-Stokes' respiration and hypertension in patients with congestive heart failure is discussed.

Lewis, J. K.: Nature and Significance of Heart Sounds and of Apex Impulses in Bundle-Branch Block. Arch. Int. Med. 53: 741, 1934.

The nature of the physical signs present in twenty patients with bundle-branch block and in three patients with "atypical" bundle-branch block has been determined by means of records of the heart sounds and apex cardiograms. Records of the heart sounds were obtained from all patients; apex cardiograms, from fourteen.

Physical signs of two distinct types occurred. Presystolic gallop rhythm was present in nine patients. In three of these patients a presystolic impulse was associated with the presystolic sound; in one the impulse was the only sign present.

A reduplicated first sound, entirely systolic, occurred in five patients. A double systolic impulse was present in one patient. A reduplicated first sound and a double systolic impulse were not found together in any of the patients studied.

The presystolic gallop rhythm present in these patients was the same as that found in persons without bundle-branch block except for a tendency for the interval between the P-wave and the gallop sound to be prolonged. The lengthening of this interval may be related to the absence of severe grades of circulatory failure in this particular group at the time of examination. The presence of gallop rhythm in bundle-branch block could be accounted for by the fact that both conditions occur in the same general type of heart disease and under the same circumstances. It could not be related to the bundle-branch block itself (or to asynchronism of the ventricles).

The incidence of gallop rhythm in the whole group was higher than that present in an unselected group of patients with degenerative heart disease. The explanation for this fact was not entirely clear, but the frequency of the anomaly appeared to be a reflection of the severity of the heart disease which accompanies bundle-branch block.

The frequency with which a reduplicated first sound occurred and its close association with the QRS complex suggest that it may be produced by asynchronism of the ventricles. However, evidence to prove or to disprove this point did not appear to be adequate.

The nature of the physical signs present was not such as to permit their use as diagnostic signs of bundle-branch block.

Harrison, W. G., Calhoun, J. A., Marsh, J. P., and Harrison, T. R.: Congestive Heart Failure. XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea. Arch. Int. Med. 53: 724, 1934.

A comparison has been made between morning and evening values of the gases in arterial blood and of respiratory and circulatory functions in a group of patients who had congestive heart failure and who suffered from dyspnea which was more marked in the evening than in the morning. The following results were obtained:

1. The oxygen capacity of the blood tended to be higher in the morning, and the oxygen saturation was usually greater in the evening. The differences were usually so slight as to be negligible.

2. Consistent variations were not observed in the hydrogen ion concentration, the carbon dioxide content or the carbon dioxide pressure of the blood. On an average the blood was slightly more alkaline in the evening and had slightly lower values for carbon dioxide content and carbon dioxide pressure.

3. No consistent alterations in heart rate or blood pressure were observed.

4. The consumption of oxygen was about 10 per cent higher in the evening than in the morning. The respiratory rate and minute ventilation were greater in the evening by an average of 15 per cent. The vital capacity was slightly lower in the evening in practically every instance, but the difference found was often not greater than the error of measurement.

5. Control observations were made on a group of patients without cardiac disease and on a group of patients with cardiac disease but without dyspnea. These two groups differed from the dyspneic subjects in the following results:

(a) Their diastolic blood pressures were usually lower in the evening than in the morning, whereas no change was observed in the patients with dyspnea.

(b) Although their increase in consumption of oxygen in the evening was of about the same degree, they exhibited no increase in respiratory rate and much smaller increases in ventilation. Likewise, the control group did not exhibit constant changes in vital capacity.

Experiments were performed on dogs in order to determine whether pulmonary congestion of such slight magnitude as to cause a barely measurable decrease in vital capacity could cause reflex stimulation of respiration. The following results were obtained:

1. In animals with intact vagus nerves the introduction of as little as 25 c.c. of blood into the left pulmonary artery (the left pulmonary veins being tied) led to a well-marked increase in respiratory rate and in ventilation.

2. Introduction of the same amount of air into the right pleural cavities of the same animals caused less marked and less sustained respiratory stimulation.

3. After bilateral vagotomy the introduction of blood or air produced no significant changes in respiration.

As a result of these clinical and experimental observations the following conclusions are drawn:

The pulmonary afferent fibers of the vagus nerve are extremely sensitive to pulmonary congestion. A very small amount of excess blood in the pulmonary vascular bed causes a well-marked reflex stimulation of breathing.

Evening dyspnea in patients with congestive heart failure is probably to be attributed to reflex respiratory stimulation and a decrease in vital capacity because of an increase in the degree of the preexisting pulmonary congestion. The greater congestion of the lungs in the evening than in the morning is believed to be due to greater bodily activity during the waking hours.

Katz, Louis N.; Soskin, Samuel; Schutz, William J.; Ackerman, Walter; and Plaut, Julian L.: **A Metabolic Exercise Tolerance Test for Patients With Cardiac Disease.** *Arch. Int. Med.* 53: 710, 1934.

A relatively simple method has been devised for measuring the excess oxygen consumption in exercise, the oxygen debt, and the recovery time. This metabolic tolerance test has been applied to a group of normal persons and to a group of patients attending the clinic for cardiac disease, and the results have been compared.

It was found that these measurements, particularly of the excess oxygen consumption of exercise, were greater than normal in patients with organic heart disease and with a history of some limitation of activity, even when no congestive heart failure was present. When these patients were classified into subgroups, according to the history of the degree of limitation of activity, the

measurements become progressively greater as one passes from the group with no limitation of activity to the group with marked limitation.

It is concluded that this test, which yields an objective quantitation of the cardiac capacity of a patient at the time of examination, merits further consideration as an adjunct in the study of cardiac disease.

Soskin, Samuel; Katz, Louis N.; Markle, Philip; and Henner, Robert: The Metabolic Exercise Tolerance Test. *Arch. Int. Med.* 53: 706, 1934.

A simplified method is described for determining the excess oxygen consumption during exercise and time required for recovery by the metabolic exercise tolerance test. The test is hardly more difficult to perform than the ordinary basal metabolism test and is suitable for routine use in the clinical laboratory. The objective nature of the test, which eliminates the subjective influence of both patient and physician, makes it particularly suitable for the accumulation of data by different observers on large groups of persons. Such an application might be made in the classification of cardiac disability for insurance purposes.

Eggleston, Cary: The Medical Treatment of the Thyrocardiac. *Am. J. M. Sc.* 187: 737, 1934.

Four clinical types of thyrocardiac disease may be distinguished: first, those patients with Graves' disease with structurally normal hearts; second, Graves' disease in patients with rheumatic heart disease; third, thyrotoxicosis in patients with arteriosclerotic or hypertensive heart disease; and fourth, patients with "masked hyperthyroidism." Emphasis is laid upon thyrotoxicosis as the common factor primarily responsible for the cardiac manifestations in all four types.

The relatively unsatisfactory results of cardiac therapy are pointed out. The keystone of successful treatment is shown to be the control of the thyrotoxic state. The minimum of risk and the maximum of success are obtained by pre-operative medical treatment, subtotal thyroidectomy at the most favorable stage, and postoperative medical treatment when necessary.

Craig, Henry R., and White, Paul D.: Etiology and Symptoms of Neuro-Circulatory Asthenia. *Arch. Int. Med.* 53: 633, 1934.

To throw more light on certain aspects of neurocirculatory asthenia (in particular, its etiology and symptoms) the analysis of 100 cases is presented, 50 without and 50 with organic heart disease. In this series of 100 cases the females outnumbered the males, 69 to 31. The average age of civilian patients is higher than that among soldiers during the war, doubtless because one is dealing with all ages in the community. The ages in our series ranged from twelve to sixty-nine years, the average age for 100 patients being $35\frac{3}{4}$ years ($31\frac{1}{2}$ years for those with pure neurocirculatory asthenia and forty years for those with complicating organic heart disease). Only 9 per cent of the 100 patients were poorly developed or undernourished. The great majority were well developed and well nourished, or obese.

Neurocirculatory asthenia may be classified etiologically:

A. (1) That which follows severe infection, operation or other illness (9 per cent of the cases). (2) That following prolonged fatiguing work or heavy strain of some other sort without respite (10 per cent of the cases).

B. (1) That following a slight to moderate infection, operation or other illness (25 per cent of the cases). (2) That following a slight to moderate amount of fatiguing work or of strain of any sort (35 per cent of the cases).

C. That occurring after little or no strain, but tending to be much aggravated by illness or fatigue (20 per cent of the cases).

The borderline between the normal and the abnormal is ill defined, but it is best indicated by the appearance of symptoms in the course of the usual physical activities and excitements of daily life, which previously gave no symptoms, or which in the average person would produce no symptoms. Neurocirculatory asthenia is to be distinguished from "irritability of the heart" alone as shown by premature beats or paroxysmal tachycardia. It is also to be distinguished from neurosis as such, in which anxiety, hypochondriasis or hysteria is predominant. Twenty-five such cases were analyzed for comparison. It differs from ordinary neurasthenia, in which the flight into disease is manifested primarily by lack of energy, easy mental and physical exhaustion, and irritability. The authors have presented data with reference to symptoms in twenty-five cases of neurasthenia. "Neurocirculatory asthenia" is a term to be preferred to "effort syndrome" in designating the condition under discussion, since effort syndrome may be produced in normal people.

Palpitation, respiratory discomfort, precordial pains, or aches and exhaustion are the four cardinal symptoms of neurocirculatory asthenia. They occur in the order named with almost the same frequency (78 to 83 per cent of the 100 cases). Radiation of the precordial discomfort of neurocirculatory asthenia to the left arm, axilla, shoulder or scapula may occur (in 33 of 74 cases of this series). The more severe the precordial discomfort, the more likely the radiation. Sighing respiration and precordial tenderness are important confirmatory signs and are almost pathognomonic of neurocirculatory asthenia.

When neurocirculatory asthenia complicates organic heart disease, the symptoms are essentially the same in character and quantity as they are in the absence of organic heart disease. The fundamental mechanism of neurocirculatory asthenia remains obscure. Variations of the same mechanism in different persons, or indeed, even different mechanisms may give rise to the different combinations of symptoms and signs.

Reichert, Frederick Leet; Rytand, David A.; and Bruck, Edwin L.: Arteriosclerosis of the Lumbar Segmental Arteries Producing Ischemia of the Spinal Cord and Consequent Claudication of the Thighs. *Am. J. M. Sc.* 187: 794, 1934.

The ordinary intermittent claudication in the arteriosclerotic is characterized by pain which is attributed to physiological processes developing in the working muscles easily fatigued due to impaired blood supply. It is associated with a lack of arterial pulsation in the feet and ankles, color alterations in the skin of the extremities on change of posture and roentgenographic evidence of calcification in the arteries of the legs.

Intermittent claudication because of weakness in the thighs and hips was the chief complaint of four nonsyphilitic arteriosclerotic patients who exhibited a spastic gait resembling that of a tabetic, who had no positive neurological signs and whose roentgenograms revealed calcification in the lower abdominal aorta.

The claudication of the thighs in these four patients was attributed to ischemia of the spinal cord produced by alterations in spinal branches of the arteriosclerotic lumbar segmental arteries arising from the abdominal aorta.

This hypothesis was strengthened by roentgenographic evidence of calcification in the terminal portion of the abdominal aorta and by experimentally produced claudication in the thighs of adult dogs after occlusion of the lumbar segmental arteries without interference with the blood supply to the thighs or remainder of the lower extremities, as shown roentgenographically by complete arterial injections of the animals.

Unilateral claudication developing after ipsilateral occlusion of one or more lumbar arteries in the dog afforded further proof that ischemia of the spinal cord was the cause of the claudication.

Krumbhaar, E. B.: Electrocardiographic Changes Accompanying Acutely Increased Pressure Following Pulmonary Artery Ligature. *Am. J. M. Sc.* 187: 792, 1934.

In an attempt to study the effect on the electrocardiogram of rapidly increased intraventricular pressures, records were taken before and after varying degrees of pressure were exerted on the pulmonary artery of anesthetized cats. The effect of increase in the pressure within the right ventricle as practiced in these experiments was regularly to increase the size of the P-wave in all Leads and frequently to produce extreme ventricular deflections like those seen in congenital heart disease. Sometimes signs similar to those of preponderance of the right ventricle appeared and disappeared when the clamp was loosed. When the clamp was about three-fourths closed, the right ventricle usually became much congested and dilated with a slow beat and the electrocardiogram sometimes showed a deep broad S_1 , a high broad R_2 , and in Lead II a deep A, medium R and no S. The possibility of such changes being due to bundle-branch block must of course be borne in mind. The T-wave, when not engulfed in the preceding S, sometimes became enlarged, sometimes inverted or diphasic, sometimes coming off near the point of R or S respectively, or at a new level from an overshoot of R (or S) or finishing at a new isoelectric period. Small extra waves, as if continuation of the T disturbance, were sometimes noted. It is suggested that changes in the ventricular complex, perhaps resembling those of right or left ventricular preponderance, especially if transient, may be due to changes in intraventricular pressure and not always to changes in muscle mass or position of the heart.

Buckbinder, William C., and Katz, Louis N.: The Electrocardiogram in Acute Experimental Distention of the Right Heart. *Am. J. M. Sc.* 187: 785, 1934.

The production of diffuse pulmonary emboli of metallic mercury following its introduction directly into the right heart or systemic venous circulation causes acute distention of the right heart. In the more chronic experiments a marked degree of right heart dilatation is regularly produced.

Instrumental compression of the pulmonary artery produces a marked ballooning out of the right side of the heart, followed soon after by a similar ballooning of the left side.

Acute distention or dilatation of the right heart in the above experiments is accompanied by no significant deviation of the electrical axis of the heart.

The peculiar aberrations of the ventricular complex (QRST) produced by mercury injection are illustrated, and evidence is presented to show that they arise because of short circuits set up by the intracardiac and extracardiac metal.

Edeiken, Joseph, and Wolferth, Charles C.: The Clinical Significance of Low T-Waves in the Electrocardiogram. *Am. J. M. Sc.* 187: 778, 1934.

A vertical or transverse position of the heart has a marked influence upon the ventricular waves of the electrocardiogram. In vertically placed hearts, R_1 is frequently low and often a low T_1 is associated. In transversely placed hearts T_3 is very frequently inverted and is sometimes associated with a low T_2 ; in many cases these findings are also associated with left axis deviation.

Although the association of low T_1 and R_1 is frequently encountered in vertical hearts, it is also found in the presence of cardiovascular damage, especially in rheumatic heart disease.

The association of a low T_1 and high R_1 is usually encountered in cases showing some cardiovascular abnormality, especially hypertension. It has, however, been observed in a few cases in which no cardiovascular abnormality was demonstrable.

The incidence of definite cardiovascular abnormality found in cases referred from wards and out-patient clinics for electrocardiographic study which could be classified in one or another of the electrocardiographic types under consideration was as follows: Type A (low T_1 and normal T_2) 83 per cent; Type B (low T_1 and T_2) 87 per cent; Type C (normal T_1 , low or flat T_2 and inverted T_3) 63 per cent. In patients derived from the same sources but with normal electrocardiograms, the incidence of definite cardiovascular abnormality found was 41 per cent.

The percentages obtained for the incidence of myocardial damage or position of the heart as the cause of the low T-waves of the type classified under A and C depend mainly on the type of material being studied. In groups of presumably normal individuals, position is the more important; in groups suspected of heart disease, myocardial damage is the more important. In certain cases with heart disease, however, the T-wave changes may be due to altered position of the heart rather than to myocardial damage per se. The authors have obtained no evidence to indicate that small T-waves in all leads may be dependent on position of the heart.

Röntgen ray study of the heart is essential in attempting to evaluate the significance of low or flat T-waves in either Lead I or Lead II of the electrocardiogram.

For guidance in the clinical interpretation of electrocardiograms the authors believe the following statements are justified:

A. An electrocardiogram with a low R_1 and low T_1 and a normal T_2 points either to abnormality of the heart or to vertical position. When the heart is vertically placed, no significance can be ascribed to these findings as evidence of cardiac abnormality. When, however, the heart occupies its usual position, the low R_1 and T_1 suggest that it may be abnormal.

B. The association of a normal or high R_1 and a low T_1 offers strong but not certain evidence of cardiac abnormality.

C. The finding of small T-waves in all leads is probably rarely if ever dependent on position of the heart. It furnishes strong presumptive evidence of abnormality of the heart.

D. The combination of a normal T_1 , a low or flat T_2 and an inverted T_3 may be due either to abnormality of the heart or to a more transverse position than is usual. When the heart is transversely placed, such an electrocardiogram may not be regarded as evidence of myocardial abnormality; when, however, the heart occupies the usual position, such a tracing suggests myocardial abnormality.

E. It is possible that in a small minority of cases, these various types of electrocardiograms may occur in the absence both of altered position of the heart and abnormality of the myocardium.

Book Review

THE SPAN OF LIFE AS INFLUENCED BY THE HEART, THE KIDNEYS AND THE BLOOD VESSELS. By Franklin R. Nuzum. Charles C. Thomas, 1933, 108 pages.

This well-made and attractive volume is designed to give information to the general public concerning varieties of cardiac disease, of Bright's disease, and of diseases of the arteries, their nature, their course, and their general management. It has become general knowledge that expectancy at birth has increased, and the reasons for the change in outlook have been attributed correctly to decrease in infant mortality and to decline in the prevalence of infectious diseases. What more natural, with these successes behind us, than to look for greater success still in the prevention and control of the "diseases" of later life? It is perhaps not ungracious to raise the question whether it is not premature to speak of certain aspects of several of these conditions as being either "diseases" or "degenerative," since there is no suitable classification of them into those which are natural processes incident to aging and those which may be regarded properly as disease or as pathological. To keep this possibility in view may save us in the sequel from serious disappointment. So far prevention, though desirable, and control have no significant successes, known to us, to their credit. How to discover them, itself awaits the development of a proper technic of analysis. But there is no reason why hope of amelioration of the state, so often unhappy, of old age should not be entertained; though the hope may be better tempered if it is bolstered by a knowledge of the facts.

In the pages of this little book there is collected an unusually large amount of knowledge without giving the impression of hurry or of undue compression. To one somewhat acquainted with its subject matter, the exposition seems lucid. But to those who have made similar attempts in brief compass to place at the disposal of laymen information on these matters, the chances of successful exposition are not too encouraging. It is the subject itself which must bear the major fault. Little is known, and much that is, is tentative; the mechanisms that are involved are just beginning to be studied and can scarcely be said to be understood. Yet there is no escape, in a society desirous of being instructed along each part of the way, from making the effort which has been made here. The amount of success which Dr. Nuzum has attained is great enough to encourage his successors to continue with the enterprise.

A. E. C.

INDEX TO VOLUME 9

A

- Abbott, W. Osler, 141*
- Abdomen, distention and release of, effect of, on blood pressures in arteries and veins, 545*
- Abnormality, congenital, heart-block with other cardiac anomalies, 96
interauricular septal defect associated with mitral stenosis, 1
- Acetyl—b—methylcholin, 140*
action of, on gastrointestinal tract in normal persons, in abdominal distention and in certain other conditions, 141*
action of, on paroxysmal tachycardia and peripheral vascular disease with a discussion of its action in other conditions, 141*
- Ackerman, Walter, Kissin, M., and Katz, L. N., 693*
- Katz, L. N., Soskin, S., Schutz, W. J., and Plaut, J. L., 825*
- Adenosine, effect of, on cardiac irregularities in man, 252
- Adrenalin, action of, in complete heart-block, 279,* 549*
- Age, advancing, relationship between anatomic changes in knee joint with, 553*
- Alexander, John, Field, H., Jr., and Barker, P. S., 298
- Allergy, importance of, in rheumatism, 101*
relation of, to general resistance in streptococcic infection, 544*
- Anderson, John P., 104*
- Anemia as cause of angina pectoris in presence of healthy coronary arteries and aorta, 690*
- Aneurysm, of innominate artery, syphilitic aortitis with, and occlusion of left carotid artery, 686
dissecting, 556 (B. R.)
- Angina pectoris, 282 (B. R.)
and cardiac asthma, induced by paroxysmal tachycardia, 133*
anemia as cause of, in presence of healthy coronary arteries and aorta, 690*
attacks of, prevention and treatment of individual, 549*
induced by paroxysmal tachycardia, simulation of coronary thrombosis by, 133*
mechanism of attacks of, effect of generalized anoxemia on electrocardiogram of normal subjects, 771
observations on production of pain and fatigue in muscular ischemia and their relationship to, 690*
paroxysm of, electrocardiographic study during, 259
therapeutic effect of total ablation of normal thyroid on congestive heart failure, 137*
treatment, continuous, of, comparative value of drugs used in, 140*
- Anoxemia, generalized, effect of, on electrocardiogram of normal subjects, its bearing on mechanism of attacks of angina pectoris, 771
- Aorta, coarctation of, sudden death due to rupture of, 533
isthmus of, stenosis of, 695*
thoracic, dynamic dilatation of, 655
- Aortitis, syphilitic, with aneurysm of innominate artery and occlusion of left common carotid artery, 686
- Arteriography, arteriovenous fistula involving common femoral artery, identified by, 817*
- Arteriosclerosis of lumbar segmental arteries producing ischemia of spinal cord and consequent claudication of thighs, 827*
- Artery, carotid, common left, occlusion of, and syphilitic aortitis with aneurysm of innominate artery, 686
coronary, paradoxical embolism of, 414
facts on disease of, based on survey of clinical and pathological record of 762 cases, 695*
in rheumatic fever, 557
occlusion, acute, electrocardiographic pattern observed following, complicated by pericarditis, 734
due to metastases from carcinoma of breast, 265
electrocardiographic study of, further observations on use of chest leads, 276*
experimental, 127*
sclerosis of, with myocardial infarction in a young woman, 539
syphilitic disease of, 421
thrombosis, acute, differentiation of, from pulmonary embolism, 692*
and diabetes, 386
early case not hitherto reported, 412
observed onset of bundle-branch block with, 677
simulation of, by angina pectoris induced by paroxysmal tachycardia, 133*
vascular communications between, and chambers of heart, nature of, 143
distribution to left and right ventricles of human heart, 165
- femoral, common, arteriovenous fistula involving, identified by arteriography, 817*
- innominate, aneurysm of, with syphilitic aortitis and occlusion of left common carotid artery, 686
- lumbar segmental, arteriosclerosis of, producing ischemia of spinal cord and consequent claudication of thighs, 827*
- pulmonary embolism, experimental, electrocardiographic findings in, 104*
differentiation of, from coronary thrombosis, 692*
ligature, electrocardiographic changes accompanying acutely increased pressure following, 828*
- sclerotic wall of, influence of, on blood pressure measurement, 134*

(An asterisk [*] after a page number indicates that the reference is an abstract and not an original article. B.R. after a page number indicates that the reference is a book review.)

- Arthritis, degenerative, relationship between anatomic changes in knee joint with advancing age, 553*
rheumatoid, comparative study of subcutaneous nodules in rheumatic fever and, 552*
erythrocytic sedimentation test in, clinical significance of, 272*
heart in, and rheumatic fever, 104*
- Asthenia, neurocirculatory, etiology and symptoms of, 826*
- Asthma, cardiac, and acute pulmonary congestion in patients with mitral stenosis, 697
and angina pectoris induced by paroxysmal auricular fibrillation and paroxysmal tachycardia, 133*
- Atropine, action of, in complete heart-block, 549*
- Aubertin, C., Lemaire, A., Donzelot, E., Clerk, A., Marchal, G., Boigey, R., Mouquin, M., Émile-Weil, P., and Tzanck, A., 142 (B. R.)
- Aufranc, Otto Elmo, and Coonse, G. K., 347
- Auricle, dilatation, extreme, of left, deformity of chest associated with, 363
rupture of, of heart, 324
experimental changes in RS-T component of electrocardiogram produced by, and by pericardial injection, 333
- Averbuck, Samuel H., 692*
- Ayerza, black cardiacs of, blood-respiratory function in, 695*
- Ayman, David, 133,* 823*
and Krakower, A., 134*
- B
- Bacal, H. L., and Struthers, R. R., 274*
- Bacon, Charles M., and Lundy, C. J., 134*
- Bain, C. W. Curtis, 822*
- Barium chloride, ephedrin sulphate and, in prevention of Stokes-Adams seizures, 821*
- Barker, Paul S., Field, H., Jr., and Alexander, J., 298
Wilson, F. N., and Johnston, F. D., 472
Wilson, F. N., Johnston, F. D., and Macleod, A. G., 447
Hill, I. G. W., and Macleod, A. G., 459
- Barnes, Arlie R., 722, 728, 734
Beaver, D. C., and Snell, A. M., 480
- Barton, E. M., and Greenwood, H. H., 128*
- Battro, Antonio, 282 (B. R.)
- Bayless, Francis, and Karsner, H. T., 557
- Beaver, Donald C., Barnes, A. R., and Snell, A. M., 480
- Bellet, Samuel, and Stewart, H. L., 533
Wood, F. C., McMillan, T. M., and Wolferth, C. C., 276*
- Berconsky, Isaac, 695*
- Berlin, David D., Blumgart, H. L., Riseman, J. E. F., and Davis, D., 137*
- Black, W. C., and Waring, J. J., 817*
- Blackford, L. Minor, and McGehee, H. M., 96
- Bland, Edward F., and Jones, T. D., 106*
- Blood flow, venous, velocity of pulmonary and peripheral, and related aspects of circulation in cardiovascular disease, 742
medical therapeutics of, 142 (B. R.)
pressure, arterial and venous, effect of abdominal distention and release of, 545*
- Blood pressure—Cont'd
in newborn, 272*
influence of sclerotic arterial wall on measurements of, 134*
of Chinese living in eastern Canada, 396
variations in tuberculosis, 694*
venous and cerebrospinal fluid pressure in cardiac failure, 823*
effects of digitalis on, of normal individuals, 138*
in thyroid dysfunction, 802
observations on practical significance of, in health and disease, 817*
pulmonary, acutely increased, following pulmonary artery ligation, electrocardiographic changes accompanying, 828*
respiratory function in black cardiacs of Ayerza, 695*
vessels, arterial, distribution to left and right ventricles of human heart, 165
perivascular reaction in lung and liver following intravenous injection of streptococci into previously sensitized animals, 552*
- Blumgart, Herrman L., 692*
Riseman, J. E. F., Davis, D., and Berlin, D. D., 137*
- Bohning, Anne, and Plaut, J. L., 500
Jochim, K., and Katz, L. N., 273*
- Boigey, R., Lemaire, A., Donzelot, E., Aubertin, C., Clerk, A., Marchal, G., Mouquin, M., Émile-Weil, P., and Tzanck, A., 142 (B. R.)
- Boller, Charles, and Hurtado, A., 129*
- Borman, M. C., Haney, H. F., and Meek, W. J., 272*
- Bowman, James E., 272*
- Brams, William A., and Golden, J. S., 802
Katz, L. N., and Kohn, L., 545*
- Bramwell, Crighton, 546*
- Breast, carcinoma of, coronary occlusion due to metastases from, 265
- Brenner, Oscar, 692*
- Brow, G. R., and Holman, D. V., 259
- Bruck, Edwin, L., Reichert, F. L., and Rytand, D. A., 827*
- Bruenn, Howard G., 421
Levy, R. L., and Kurtz, D., 691*
- Buckbinder, William C., and Katz, L. N., 828
- Bunta, Emil, 694*
- Burton, Eleanor P., and Howell, K. M., 102*
- C
- Calhoun, J. Alfred, Harrison, W. G., and Harrison, T. R., 820*
Marsh, J. P., and Harrison, T. R., 824*
- Camero, Anthony R., Hitchcock, C. H., and Swift, H. F., 552*
- Campbell, Maurice, and Suzman, S. S., 304
- Capacity, pulmonary, total, change with body posture, 131*
correlation with physical and radiological measurements, 130*
normal, absolute and relative values, 129*
preliminary observations on cases of pulmonary emphysema and pneumoconiosis, 131*
- Capillaries, human, in health and disease, 273*
- Carcinoma of breast, coronary occlusion due to metastases from, 265

- Cerebrospinal fluid pressure and venous pressure in cardiac failure, 823*
- Chamberlain, C. T., Griffith, G. C., and Kitchell, J. R., 544,* 817*
- Chest, deformity of, associated with extreme dilatation of left auricle, 363
expiratory position of, in man, influence of some ordinary activities on, plethysmographic study of and quiet breathing, 129*
- Chester, William, and Schwartz, S. P., 105*
- Children, cardiac, convalescent care of, 106*
rheumatic manifestations in subacute bacterial endocarditis in, 29
- Chinese, blood pressure of, in eastern Canada, 396
- Chordae tendineae, rupture of, of mitral valve, 492
- Chorea, course and prognosis of, and rheumatic fever, 106*
- Circulation, coronary, coronary pressure pulses and their interpretation, 272*
effect on, of acute experimental hypervolemia, 545*
in cardiovascular disease, velocity of pulmonary and peripheral venous blood flow and related aspects of, 742
mechanism of relation of intrapleural pressure to, 347
peripheral, in acute lobar pneumonia, 821*
pulmonary, 692*
obstruction in, syndrome of, 817*
speed of, observations on, 822*
- Cisternal pressure in congestive heart failure and its bearing on orthopnea, 275
- Clark, Gurney, Grollman, A., Friedman, B., and Harrison, T. R., 132*
- Claudication of thighs, arteriosclerosis of lumbar segmental arteries producing ischemia of spinal cord and, 827*
- Clawson, B. J., 544*
- Clerk, A., Lemaire, A., Donzelot, E., Aubertin, C., Marchal, G., Bolgey, R., Mouquin, M., Emile-Well, P., and Tzanck, A., 142 (B. R.)
- Clowe, G. M., Kellert, E., and Gorham, L. W., 324
- Coburn, Alvin E., 132*
- Coggeshall, H. C., and Greene, J. A., 129*
- Cohn, Alfred E., and Lingg, C., 283
- Comroe, Bernard I., 680
- Condenser, effect of, in electrocardiogram, 517
- Congenital abnormality, heart-block, 96
interauricular septal defect, associated with mitral stenosis, 1
- Congestion, acute pulmonary, and cardiac asthma in patients with mitral stenosis, 697
- Convalescent care of cardiac children, 106*
- Cooley, Laurence E., and McNamara, F. P., 686
- Coonse, G. Kenneth, and Aufranc, O. E., 347
- Cotton, F. S., and Wiggers, C. J., 272*
- Cowan, Donald W., 378
- Craig, Henry R., and White, P. D., 826*
- Crane, Martin P., and Leplace, L. B., 690*
- Crawford, Baxter L., and Mahler, H. K., 548*
- Creatine concentration, difference in, of left and right ventricular cardiac muscle, 819*
content of myocardium of normal and abnormal human hearts, 378
- Crittenden, P. J., Maher, C. C., and Shapiro, P. F., 664
- Crummer, Leroy, obituary, 418
- Cullen, Glenn, E., and Wilkins, W. E., 274

D

- Daughton, A. D., Hart, A. D., and Wood, J. E., 690
- Davis, Austin C., and Smith, H. L., 81
- Davis, David, and Weiss, S., 45
Blumgart, H. L., Riseman, J. E. F., and Berlin, D. D., 137*
- Dawson, M. H., 552*
- de la Chapelle, Clarence, Graef, I., and Rottino, A., 103*
- Death, cause of, clinical notes on rheumatic heart disease with special reference to, 278*
sudden, due to rupture of aorta with coarctation, 533
- Dermatitis, exfoliative, acute diffuse myocarditis following, 813
- Diabetes and coronary thrombosis, 386
- Diastole, phases of, observations on duration of, in man, 500
- Digitalis and diphtheria toxin, alleged antagonism between, 549*
cumulation of, observation on nature of, in ambulatory patients with cardiac disease, 279*
dose, clinical, and effects of, assayed by pigeon method, 248
effect of, on venous pressure of normal individuals, 138*
specialties, comparative potency of, according to pigeon method, 138*
studies on, in ambulatory patients with cardiac disease, further observations on nature of cumulation, 279*
- Diphtheria toxin and digitalis, alleged antagonism between, 549*
- Diuretics, action of, studies on, 139*
- Dock, William, 128*
- Donzelot, E., Lemaire, A., Aubertin, C., Clerk, A., Marchal, G., Bolgey, R., Mouquin, M., Emile-Well, P., Tzanck, A., 142 (B. R.)
- Dresbach, M., Randles, F. S., and Gorham, L. W., 333
- Duryee, A., Wilbur, and Wright, I. S., 273*
- Dyson, John M., 764
- Dyspnea, evening, reflex stimulation of respiration as cause of, 824
nocturnal, clinical types, 820*

E

- Edeiken, Joseph, and Wolferth, C. C., 828*
- Eggleston, Cary, 826
- Electrocardiogram, apparatus for simultaneous and arterial pulse records, 530
changes accompanying acutely increased pulmonary pressure following pulmonary artery ligation, 828*
correlation of initial deflections of ventricular complex with situation of acute myocardial infarction, 728

Electrocardiogram—Cont'd

- effect of condensers in, 517
- effect of generalized anoxemia on, of normal subjects, its bearing on mechanism of attacks of angina pectoris, 771
- findings in experimental pulmonary embolism, 104*
- form of, in experimental myocardial infarction; septal infarcts and origin of preliminary deflections of canine levocardiogram, 596
- huge T-waves in precordial leads in cardiac infarction, 706
- in acute experimental distention of right heart, 828*
- initial complex of, after infarction of human heart, 616
- interpretation of lead inversion in bundle-branch block, 72
- large Q-waves in Lead III, 694*
- observation on carotid sinus reflex, 782
- pattern observed following acute coronary occlusion complicated by pericarditis, 734
- precordial lead in normal adults, 511
- Q and T types of, their comparative and complimentary value in indicating occurrence of acute myocardial infarction, 722
- QRS complex, duration of, in normal and abnormal, 642
- identification of separate complexes of, 238
- representing potential variations of a single electrode, 417
- RS-T component, changes in, produced by experimental rupture of auricle of dog's heart and by pericardial injection, 333
- RS-T segment, changes in, relation between position of experimental myocardial lesion in dog and, 272*
- self-retaining skin contact electrode for chest leads in, 526
- significance, clinical, of low T-waves in, 828*
- significance of, characterized by, on abnormally long QRS interval and by broad S deflections in Lead I, 459
- significance of ventricular preponderance and T-wave inversion in human, 693*
- study during a paroxysm of angina pectoris, 259
- study of coronary occlusion, further observations on chest leads, 276*
- study of viscerocardiac reflexes during major operations, 664
- type of, unusual, in right bundle-branch block, 472
- voltage, low, 405
- Electrode, self-retaining skin contact for chest leads in electrocardiography, 526
- Electrolytes in human tissue, comparison of normal hearts with hearts showing congestive heart failure, 274*
- Elliot, Albert H., 690*
- Elliott, Arthur R., and Fenn, G. K., 806
- Ellis, Laurence B., and Weiss, S., 139*
- Elsom, K. A., Starr, I., and Reisinger, J. A., 140*
- Embolism of pulmonary artery, experimental, electrocardiographic findings in, 104*
- Émile-Weil, P., Lemaire, A., Donzelot, E., Aubertin, C., Clerc, A., Marchal, G., Boigey, R., Mouquin, M., and Tzanck, A., 142 (B. R.)
- Emphysema, pulmonary, observation on, and pneumoconiosis, 131*
- Endocarditis, subacute bacterial, in children, rheumatic manifestations in, 29
- gonococcus, diagnosis of, 134*
- Enklewitz, Morris, 386
- Ephedrin, Stokes-Adams disease treated with, 90
- sulphate and barium chloride in prevention of Stokes-Adams seizures, 821*
- Eppinger, Eugene C., and Midelfort, P. A. H., 695*
- Evans, William, and Hoyle, C., 140,* 549*
- Exercise tolerance test, metabolic, for patients with cardiac disease, 825,* 826*
- Exudate, cytological studies of granulomata and, from patients with rheumatic fever, 101*
- Eyster, J. A. E., and Hicks, E. V., 544*

F

- Fardy, Ann, 105*
- Fatigue, observation on production of pain and, in muscular ischemia and their relationship in angina pectoris, 690*
- Feil, H. S., and Stone, C. S., 53
- Fenn, George Karl, and Elliott, A. R., 806
- Fibrillation, auricular, paroxysmal, and paroxysmal tachycardia, angina pectoris and cardiac asthma induced by, 133*
- paroxysms of, prevention of, use of quinidine in ambulatory patients for, with especial reference to dosage and effects on intraventricular conduction, 219
- pathological changes in heart in, 548*
- relationship of, to mitral stenosis and certain rheumatic tissue changes, 103*
- ventricular transient, 818,* 819*
- action of quinine and quinidine in patients with, 792
- Field, Henry, Jr., Barker, P. S., and Alexander, J., 298
- Fistula, arteriovenous, involving common femoral artery, identified by arteriography, 817*
- France, Richard, 694*
- Frankel, A., 419 (B. R.)
- Fray, Walter W., and Hurtado, A., 130,* 131*
- and McCann, W. J., 131*
- Friedlander, Alfred, 212
- Friedman, Ben, Grollman, A., Clark G., and Harrison, T. R., 132*
- Frothingham, Channing, and Hass, G. M., 492
- Flutter, auricular, paroxysm of, prevention of, use of quinidine in ambulatory patients for, with especial reference to dosage and effects on intraventricular conduction, 219

G

- Gentile, R. J., and Wood, J. E., Jr., 530
- Gibbon, John H., and Landis, E. M., 277*
- Gilchrist, A. Rae, 279,* 549,* 556,* 821*
- Glucose therapy in heart failure in advanced heart disease, 437
- Gold, Harry, and Klumpp, M. M., 549*
- Otto, H. L., and Messelhoff, C. R., 279*
- Satchwell, H., 219
- Goldbloom, A. Allen, 818*

- Golden, J. S., and Brams, W. A., 802
 Goldsmith, Melville A., Stroud, W. D.,
 Polk, D. S., and Thorp, F. Q.,
 135*
 Gorham, L. W., Clowe, G. M., and Kel-
 lert, E., 324
 Randles, F. S., and Dresbach, M., 333
 Graef, Irving, de la Chapelle, C., and
 Rottino, A., 103*
 Granulomata, cytological studies of, and
 exudates from patients with
 rheumatic fever, 101*
 Greene, J. A., and Coggeshall, H. C., 129*
 Greenwood, H. H., and Barton, E. M.,
 128*
 Gregg, D. E., and Wiggers, C. J., 545*
 Griffith, George C., Chamberlain, C. T.,
 and Kitchell, J. R., 544,* 817*
 Grollman, Arthur, Friedman, B., Clark,
 G., and Harrison, T. R., 132*
 Gross, Louis, and Kugel, M. A., 165
 Rothschild, M. A., and Kugel, M. A.,
 586

H

- Hallock, Phillip, 196
 Hamburger, Walter W., Katz, L. N., and
 Schutz, W. J., 771
 Haney, Hance F., Borman, M. C., and
 Meek, W. J., 272*
 Hanzlik, P. J., and Lehman, A. J., 138*
 Harrison, T. R., Grollman, A., Friedman,
 B., and Clark, G., 132*
 Harrison, W. G., and Calhoun, J. A.,
 820*
 and Marsh, J. P., 824*
 Harrison, William Groce, Jr., 275,* 823*
 Calhoun, J. A., and Harrison, T. R.,
 820*
 Marsh, J. P., and Harrison, T. R.,
 824*
 Hart, Andrew D., Wood, J. E., and
 Daughton, A. D., 690*
 Hass, George M., and Frothingham, C.,
 492
 Health, public heart disease from point
 of view of, 283
 Heart, arrhythmia, 282 (B. R.)
 block, ephedrin sulphate and barium
 chloride in prevention of
 Stokes-Adams seizures, 821*
 auriculoventricular, complete par-
 oxysmal, 267
 bundle branch, 548
 electrocardiographic appearance
 of, in man, effect of heart's
 position on, 693*
 interpretation of lead inversion
 in, 72
 nature and significance of heart
 sounds and of apex impulse in,
 821*
 observed onset of, with coronary
 thrombosis 45 hours later, 677
 right, electrocardiograms of, un-
 usual type in, 472
 complete, action of adrenalin in, 279,*
 550*
 action of atropine in, 549*
 congenital, 304
 in hyperthyroidism following acute
 infections, 81
 treated with ephedrin, 90
 congenital, with other cardiac anom-
 alies, 96
 transient, observation on alteration
 in rhythm of heart preceding
 syncope seizure in a woman
 with, 819*
 chambers of, vascular communications
 between coronary arteries and,
 nature of, 143

Heart—Cont'd

- contraction, duality of, 556 (B. R.)
 premature, ventricular left, from elec-
 trical stimulation of exposed
 human heart, 131*
 dilatation and hypertrophy in infants
 and young children, 136*
 disease, advanced, glucose therapy in
 heart failure in, 437
 ambulatory patients with, studies on
 digitalis in further observations
 on nature of cumulation of
 digitalis, 279*
 and thyroid disease, medical treat-
 ment of, 826*
 in children, convalescent care, 106*
 factors causing clinical jaundice in,
 135*
 from point of view of public health,
 283
 in pregnancy, 692*
 pulmonary, in pneumoconiosis, 764
 radiology in, 546*
 rheumatic, clinical conception of, 26
 clinical notes on, with special refer-
 ence to cause of sudden death
 in, 278*
 emboli, manifestations of, in, 45
 incidence and significance of ac-
 tive infection in cases of, dur-
 ing various age periods, 586
 lesions of kidney associated with,
 105*
 manifestation of, in subacute bac-
 terial endocarditis in children,
 29
 in southern Florida, 63
 ten years' observations of children,
 135*
 enlargement, radiological diagnosis of,
 546*
 failure, cerebrospinal fluid pressure and
 venous pressure in, 823*
 clinical types of nocturnal dyspnea,
 820*
 critical study of methods for de-
 termining cardiac output in pa-
 tients with cardiac disease,
 132*
 electrolyte in human tissue, com-
 parison of normal hearts with
 hearts showing, 274*
 reflex stimulation of respiration as
 cause of evening dyspnea, 824*
 therapeutic effect of total ablation
 of normal thyroid on, and
 angina pectoris, 137*
 congestive, cisternal pressure in, and
 its bearing on orthopnea, 275*
 glucose therapy of, in advanced heart
 disease, 437
 hypertrophy and dilatation in infants
 and young children, 136*
 of unknown etiology in young adults,
 178
 impulse apex, nature and significance
 of heart sounds and, in bundle-
 branch block, 824
 in myxedema, 196
 in rheumatic fever and rheumatoid
 arthritis, 104*
 infarction, huge T-waves in precordial
 leads in, 706
 correlation of initial deflection of ven-
 tricular complex with situation
 of, 728
 Q and T types of electrocardiogram,
 722
 irregularities in man, effect of adeno-
 sine, 252
 medical therapeutics, 142 (B. R.)
 muscle, ventricular left and right, dif-
 ference in creatine concentra-
 tion of, 819*
 output, critical study of methods for
 determining, in patients with
 cardiac disease, 132*

Heart, output—Cont'd

- effect of respiration on, 544*
 - pathological changes in, in auricular fibrillation, 548*
 - position, effect of, on electrocardiographic appearance of bundle-branch block in man, 643*
 - preponderance, ventricular right, of, 693*
 - right, distention of, acute experimental, electrocardiogram in, 828*
 - sarcoma, primary, 480
 - sound, mode of production of, 128*
 - nature and significance of, and apex impulse in bundle-branch block, 824*
 - stimulus, internal, origin of, 119
- Hemopericardium, 680
- Hemorrhages, paroxysmal pulmonary, with mitral stenosis, 14
- Henner, Robert, Soskin, S., Katz, L. N., and Markle, P., 826*
- Henrijean, F., 556 (B. R.)
- Heredity in arteriolar hypertension, 823*
- Hicks, Earl V., and Eyster, J. A. E., 544*
- Higley, Charles S., and Stecker, R. M., 90
- Hilbert, Eunice H., and Seham, M., 275*
- Hill, Ian G. W., Wilson, F. N., and Johnston, F. D., 596
- Macleod, A. G., and Barker, P. S., 459
- Hirsch, I. Seth, 822*
- Hitchcock, Charles H., Camero, A. R., and Swift, H. F., 552*
- Holman, Delavan V., and Brow, G. R., 259
- Holt, Evelyn, 363
- Horton, Bayard T., 817*
- Howell, Katharine M., and Burton, E. P., 102*
- Hoyle, Clifford, 276*
- and Evans, W., 140,* 549*
- Hurtado, Alberto, and Boller, C., 129*
- and Fray, W. W., 130,* 131*
- Fray, W. W., and McCann, W. S., 131*
- Hurwitz, David, Solomon, P., Woodall, M., and Lamb, M. E., 134*
- Hurxthal, Lewis M., 238
- Hypertension, arteriolar, essential, personality type of patients with, 133*
- heredity in, 823*
- pituitary secretion in, 276*
- Hyperthyroidism, complete heart-block in, following acute infection, 81
- Hypervolemia, experimental acute, circulatory effect of, 545*

I

- Infants, heart dilatation and hypertrophy in, and young children, 136*
- Infarction, experimental, of interventricular septum, 128*
- myocardial acute, correlation of initial deflections of ventricular complex with situation of, 728
- Q and T type of electrocardiogram, their comparative and complementary value in indicating occurrence of, 722
- experimental, form of electrocardiogram in, 596*
- in a young woman, sclerosis of coronary arteries, 539
- of heart, huge T-wave in precordial leads in, 706
- human, initial complexes of electrocardiogram after, 516

Irwin, Ralph L., Keefer, C. S., Parker, F., Jr., and Myers, M. K., 553,* 821*

Ischemia, muscular, observations on production of pain and fatigue in, and their relationship in angina pectoris, 690*

of spinal cord, arteriosclerosis of lumbar segmental arteries producing, and consequent claudication of thighs, 827*

J

- Jacobi, Mendel, Kenler, M., and Silverman, I., 414
- Jaffe, Harry L., and Master, A. M., 104*
- Jaundice, clinical, in heart disease, factors causing, 135*
- Jezer, Abraham, and Schwartz, S. P., 252, 792, 818,* 819*
- Oppenheimer, B. S., and Schwartz, S. P., 252
- Jochim, Kenneth, Bohning, A., and Katz, L. N., 273*
- Johnston, Franklin D., Wilson, F. N., and Barker, P. S., 472
- and Hill, I. G. W., 596
- Macleod, A. G., and Barker, P. S., 447
- Hill, I. G. W., Macleod, A. G., and Barker, P. S., 459
- Jones, T. Duckett, and Bland, E. F., 106*
- and McBroom, J., 102*
- Jordan, Edwin P., 101*

K

- Karsner, Howard T., and Bayless, F., 557
- Katz, Louis N., and Buckbinder, W. C., 828*
- Bohning, A., and Jochim, K., 273*
- Brams, W. A., and Kohn, L., 545*
- Hamburger, W. W., and Schutz, W. J., 771
- Kissin, M., and Ackerman, W., 693*
- Markle, F., and Henner, R., 826*
- Soskin, S., Schutz, W. J., Ackerman, W., and Plaut, J. L., 825*
- Keefer, Chester S., Parker, F., Jr., Myers, W. K., and Irwin, R. L., 553,* 821*
- Kellert, E., Clowe, G. M., and Gorham, L. W., 324
- Kellogg, Frederick, and Prinzmetal, M., 370
- Kenler, Maurice, Jacobi, M., and Silverman, I., 414
- Kerley, Peter, 546*
- Kidney, lesions of, associated with rheumatic heart disease, 105*
- King, John T., 548*
- Kissin, Milton, and Schwarzschild, M., 517
- Ackerman, W., and Katz, L. N., 693*
- Kitchell, J. R., Griffith, G. C., and Chamberlain, C. T., 544,* 817*
- Klumpp, Margaret M., and Gold, H., 549*
- Theodore, G., Wearn, J. T., Mettler, S. R., and Zschesche, L. J., 143
- Knee joint, histological changes in, with advancing age, 821*
- Kohn, J., Brams, W. A., and Katz, L. N., 545*
- Krakower, A., and Ayman, D., 134*
- Krumbhaar, E. B., 828*

- Kugel, M. A., and Gross, L., 165
and Lichtman, S. S., 135*
and Stoloff, E. G., 136*
Rothschild, M. A., and Gross, L., 586
Kurtz, Dorothy, Levy, R. L., and Bruenn,
H. G., 695*
Kymphonoroentgenography, 822*

L

- Lamb, Arthur, E., 692*
Marion, E., Solomon, P., Hurwitz, D.,
and Woodall, M., 134*
Landis, Eugene M., and Gibbon, J. H.,
277*
Laplace, Louis B., and Crane, M. P., 690*
Larson, L. M., and Peppard, T. A., 265
Laws, Clarence L., and Levine, S. A.,
278*
Leads, chest, self-retaining skin contact
electrodes for, in electrocardi-
ography, 526
clinical evaluation of Lead IV, 818*
precordial, in normal adults, 511
in cardiac infarction, huge T-waves
in, 706
Lehman, A. J., and Hanzlik, P. J., 138*
Lemaire, A., Donzelot, E., Aubertin, C.,
Clerk, A., Marchal, G., Boigey,
R., Mouquin, M., Émile-Weil, P.,
and Tzanck, A., 142 (B. R.)
Levine, Samuel A., 26
and Laws, C. L., 278*
Levy, Robert L., and Rousselot, L. M.,
178
Bruenn, H. G., and Kurtz, D., 691*
Lewis, J. K., 824*
Lichtman, S. S., and Kugel, M. A., 135*
Life, span of, as influenced by heart,
kidneys and blood vessels, 880
(B. R.)
Linegar, Charles R., Seecof, D. P., and
Myers, V. C., 819*
Lingg, Claire, and Cohn, A. E., 437
Lundy, Clayton J., and Bacon, C. M.,
134*
Luten, Drew, and Smith, A. E., 437

M

- Mackinnon, A. V., 547*
Macleod, A. Garrard, Wilson, F. N., John-
son, F. D., and Barker, P. S.,
447
Maher, C. C., Crittenden, P. J., and
Shapiro, P. F., 664
Sullivan, C. P., and Scheribel, C. P.,
548*
Mahler, Henry K., and Crawford, B. L.,
548
Marchal, G., Lemaire, A., Donzelot, E.,
Aubertin, C., Clerk, A., Boigey,
R., Mouquin, M., Émile-Weil, P.,
and Tzanck, A., 142 (B. R.)
Markle, Philip, Soskin, S., Katz, L. N.,
and Henner, R., 826*
Marsh, J. P., Harrison, W. G., Calhoun,
J. A., and Harrison, T. R., 824*
Martinez, Gregorio N., 282 (B. R.)
Master, Arthur M., 511, 693*
and Jaffe, H. L., 104*
McBroom, Josephine, and Jones, T. D.,
102*
McCann, William S., Hurtado, A., and
Fray, W. W., 131*
McCulloch, Hugh, 106*
McDonald, A. C., and McDonald, C. H.,
119

- McEwen, Currier, 101*
McGehee, Henry M., and Blackford, L.
M., 96
McGinn, Sylvester, and White, P. D., 1,
642, 697
McMillan, Thomas M., Wood, F. C., Bel-
let, S., and Wolferth, C. C., 276*
McNamara, Frank P., and Cooley, L. E.,
686
Meek, Walter J., Haney, H. F., and Bor-
man, M. C., 272*
Messelhoff, Charles R., Otto, H. L., and
Gold, H., 279*
Mettier, Stacy R., Wearn, J. T., Klumpp,
T. G., and Zschiesche, L. J., 143
Midelfort, Peter A. H., and Eppinger,
E. C., 695*
Mitral valve, stenosis of, interauricular
septal defect associated with, 1
paroxysmal pulmonary hemorrhage
in, 14
relationship of auricular fibrillation
to, and certain rheumatic tissue
changes, 163*
Mouquin, M., Lemaire, A., Donzelot, E.,
Aubertin, C., Clerk, A., Marchal,
G., Boigey, R., Émile-Weil, P.,
and Tzanck, A., 142 (B. R.)
Murmur, flint, production of, anatomic
mechanism in, 547*
Myers, Victor C., Seecof, D. P., and Line-
gar, C. R., 819*
Myers, Walter K., Keefer, C. S., Parker,
F., Jr., and Irwin, R. L., 553,*
821*
Myocarditis, diffuse acute, following ex-
foliative dermatitis, 813
Myocardium, chronaxie, new method for
determination of, 281 (B. R.)
creatine content of normal and ab-
normal human hearts, 378
infarction, experimental of, form of
electrocardiogram in, 596
acute, of, Q and T types of electro-
cardiogram, comparative and
complimentary value in indicat-
ing occurrence of, 722
correlation of initial deflections of
ventricular complex with situa-
tion of, 728
in a young woman, sclerosis of cor-
onary arteries with, 539
lesion in, experimental, relation be-
tween position of, in dogs and
change in RS-T segment of elec-
trocardiogram, 272*
thebesian vessels as source of nourish-
ment for, 273*
Myxedema, heart in, 196

N

- Nelson, Robert Lyman, 813
Nerve, vagus, unusual sinus tachycardia
with observations on vagal ac-
tivity by direct stimulation of,
in man, 298
Newborn, blood pressure in, 272*
Nichol, A. D., 72
Nichol, E., Sterling, 63
Nicholls, Edith E., 273*
Nodules, subcutaneous, comparative study
of, in rheumatic fever and rheu-
matoid arthritis, 552*

O

- Oppenheimer, B. S., and Schwartz, S. P.,
14
Jezer, A., and Schwartz, S. P., 252

- Orthopnea, cisternal pressure in congestive heart failure and its bearing on, 275*
- Oscillometry, studies in, 212
- Otto, Harold L., Gold, H., and Messelhoff, C. R., 279*
- and Satchwell, H., 219

P

- Pain, observation on production of, and fatigue in muscular ischemia and their relationship in angina pectoris, 690*
- Pal, J., 696 (B. R.)
- Parker, Frederic, Jr., Keefer, C. S., Myers, W. K., and Irwin, R. L., 553,* 821*
- Parkinson, John, 546*
- Peppard, T. A., and Larson, L.M., 265
- Pericarditis, electrocardiographic pattern observed following acute coronary occlusion complicated by, 734
- Pericardium, injection of, changes in RS-T component of electrocardiogram produced by experimental rupture of auricle of dog's heart and by, 333
- Perry, C. Bruce, 677, 821*
- Pigeon, assay method of digitalis, clinical dose and effects of, 248
- Pituitary secretion in high blood pressure, 276*
- Plaut, John L., and Bohning, A., 500
- Katz, L. N., Soskin, S., Schutz, W. J., and Ackerman, W., 825*
- Pleural pressure, relation of, to mechanics of circulation, 347
- Pneumoconiosis, observation on, and pulmonary emphysema, 131*
- pulmonary heart disease in, 764
- Pneumonia, lobar, acute, peripheral circulation in, 821*
- Polk, D. Stewart, Stroud, W. D., Goldsmith, M. A., and Thorp, F. Q., 135*
- Posture, body, changes in total pulmonary capacity with, 131*
- Precipitin reactions in blood of rheumatic patients following acute throat infections, 554*
- Pregnancy, heart disease in, 692*
- Prinzmetal, Myron, and Kellogg, F., 370
- Pulse, arterial, apparatus for simultaneous electrocardiograms and records of, 530
- jugular, significance of, in clinical diagnosis of ventricular tachycardia, 370
- pressure, coronary, and interpretation, 272*
- Purks, W.K., 655

Q

- Quinidine, action of, and quinine on patients with transient ventricular fibrillation, 792
- use of, in ambulatory patients for prevention of paroxysms of auricular flutter and fibrillation with especial reference to dosage and effect on intraventricular conduction, 219
- Quinine, action of, and quinidine on patients with transient ventricular fibrillation, 792

R

- Radiology of heart disease, 516*
- Randles, F. S., Gorham, L. W., and Dresbach, M., 333
- Rathe, H. W., 539
- Reflex carotid sinus, electrocardiographic observations on, 782
- viscerocardiac, during major operation, electrocardiographic study of, 664
- Reichert, Frederick L., Ryland, D.A., and Bruck, E. L., 827*
- Reisinger, J. A., Starr, I., and Elsom, K. A., 140*
- Respirations, effect of, on cardiac output, 544*
- influence of determination of basal metabolism on respiratory movements in man and effect of these alterations on calculated basal metabolic rate, 129*
- quiet breathing, study of, and influences of some ordinary activities on expiratory position of chest in man, 129*
- reflex stimulation of, as cause of evening dyspnea, 824*
- Rheumatic fever, bacteriological study of throats in, with special reference to hemolytic streptococci, 102,* 553*
- comparative study of subcutaneous nodules in, and rheumatoid arthritis, 552*
- coronary arteries in, 557
- course and prognosis of, and chorea, 106*
- cytological studies of granulomata and exudate from patients with, 101*
- determination of activity of, in childhood, 274*
- dissociation of streptococci obtained from, 102*
- etiology of, 102*
- heart in, and rheumatoid arthritis, 104*
- tissue changes, relationship of auricular fibrillation to mitral stenosis and, 103*
- in Piedmont, Virginia, incidence and clinical manifestation, 690*
- precipitin reactions in blood of, following acute throat infections, 554*
- relationship of, to development of alteration of tissues, 132*
- skin lesions in, 105*
- Rheumatism, importance of allergy in, 101*
- muscular, in childhood, 275*
- Riseman, Joseph E. F., Blumgart, H. L., Davis, D., and Berlin, D.D., 137*
- Robb, George P., and Weiss, S., 742
- Roesler, Hugo, 692*
- Rosenthal, Maurice, 647
- Roth, Irving R., 526
- Rothschild, M. A., Kugel, M.A., and Gross, L., 586
- Rottino, Antonio, de la Chappelle, C., and Graef, L., 103*
- Rousselot, Louis M., and Levy, R. L., 178
- Rupture of right auricle of heart, 324
- experimental, changes in RS-T component of electrocardiogram produced by, and by pericardial injection, 333
- Ryland, David A., 138*
- Reichert, F. L., and Bruck, E. L., 827*

S

- Sachs, Adolph, and Traynor, R. L., 267
 Salyrgan, effect of, upon water content of plasma as measured by refractive index, 139*
 Saphir, O., and Wile, S. A., 29
 Sarcoma, primary, of heart, 480
 Satchwell, Harry, 141*
 Gold, H., and Otto, H. L., 219
 Scheribel, C. P., Maher, C. C., and Sullivan, C. P., 548*
 Schlesinger, Bernard, and Signy, A. G., 554*
 Schmitz, Henry Lenzen, 139*
 Schutz, W. J., Katz, L. N., and Hamburger, W. W., 771
 Soskin, S., Ackerman, W., and Plaut, J. L., 825*
 Schwartz, Sidney P., and Chester, W., 105*
 and Oppenheimer, B. S., 14
 Jezer, A., and Oppenheimer, 252, 792, 818,* 819*
 Schwarzschild, Myron, and Kissin, M., 517
 Seecof, David P., Linegar, C. R., and Myers, V. C., 819
 Sedimentation erythrocyte test, clinical significance of, in rheumatoid arthritis, 273*
 Seham, Max, and Hilbert, E. H., 275*
 Septum, interventricular, experimental infarction, of, 128*
 Shapiro, P. F., Maher, C. C., and Crittenden, P. J., 664
 Shennan, T., 556 (B. R.)
 Sigler, Louis H., 782
 Signy, A. Gordon, and Schlesinger, B., 554*
 Silverman, Irving, Jacobi, M., and Kenler, M., 414
 Skin, lesion of, in rheumatic fever, 105*
 Smith, Abigail Eliot, and Luten, D., 437
 Smith, Harry, L., and Davis, A. C., 81
 Snell, Albert M., Barnes, A. R., and Beaver, D. C., 480
 Sodium nitrite, influence of, on cardiovascular system and on renal activity, 139*
 Solomon, Philip, Hurwitz, D., Woodall, M., and Lamb, M. E., 134*
 Soskin, Samuel, Katz, L. N., Markle, P., and Henner, R., 826*
 Schutz, W. J., Ackerman, W., and Plaut, J. L., 825*
 Spinal cord, ischemia of, arteriosclerosis of lumbar segmental arteries producing, and consequent claudication of thighs, 827*
 Sproull, John, 133*
 Stainsby, Wendell J., and Nicholls, E. E., 273*
 Starr, I., Elsom, K. A., and Reisinger, J. A., 140*
 Stecker, Robert M., and Higley, C. S., 90
 Steuer, Leonard G., 405
 Stewart, Harold L., and Bellet, S., 533
 Stockton, A. B., 248
 Stokes-Adams disease (see Heart-block, complete)
 seizures, ephedrine sulphate and bromine chloride in the prevention of, 821*
 Stoll, Henry F., 412
 Stoloff, E. Gordon, and Kugel, M. A., 136*
 Stone, C. S., and Feil, H. S., 53

- Streptococcus, dissociation of, obtained from acute rheumatic fever, 102*
 hemolyticus, bacteriological study of throats in rheumatic and non-rheumatic fever cases with special reference to, 102,* 553*
 infection, relation of allergy to general resistance, in, 544*
 injection, intravenous, of, into previously sensitized animals, perivascular reactions in lung and liver following, 552*
 Strophanthin therapy, 419 (B. R.)
 Stroud, William D., Goldsmith, M. A., Polk, D. S., and Thorp, F. Q., 135*
 Struthers, R. R., and Bacal, H. L., 274*
 Styron, Norman C., and Weinstein, I., 102,* 553*
 Sullivan, C. P., Maher, C. C., and Scheribel, C. P., 548*
 Suzman, S. S., and Campbell, M., 304
 Swift, Homer F., Hitchcock, C. H., and Camero, A. R., 552*
 Syphilis of coronary arteries, 421

T

- Tachycardia, paroxysmal, and paroxysmal auricular fibrillation, angina pectoris and cardiac asthma induced by, 133*
 angina pectoris induced by, simulation of coronary thrombosis, 133*
 rhythm of, 547*
 sinus, unusual, with observations on vagal activity, 298
 ventricular, significance of jugular pulse in clinical diagnosis of, 370
 long continued, 806
 Thebesian vessels as source of nourishment for myocardium, 273*
 Thorp, Francis Q., Stroud, W. D., Goldsmith, M. A., and Polk, D. S., 135*
 Thyroid disease and heart disease, medical treatment of, 826*
 dysfunction, venous pressure in, 802
 gland, normal, total ablation of, therapeutic effect of, on congestive heart failure and angina pectoris, 137*
 Traynor, Raymond L., and Sachs, A., 267
 Tuberculosis, blood pressure variations in, 694*
 Tzanck, A., Lemaire, A., Donzelot, E., Aubertin, C., Clerk, A., Marchal, G., Boigey, R., Mouquin, M., and Emile-Weil, P., 142 (B. R.)

V

- Valve, mitral, rupture of normal chordae tendineae of, 492
 stenosis of, acute pulmonary congestion and cardiac asthma in patients with, 697
 interauricular septal defect associated with, 1
 paroxysmal pulmonary hemorrhage in, 14
 relationship of auricular fibrillation to, and certain rheumatic tissue changes, 163*
 Van Bogaert, Adalbert, 281 (B. R.)
 Vasodilatation, method for producing, in lower extremities, 277*

W

- Waring, James J., and Black, W. C., 817*
 Wearn, Joseph T., Mettier, S. R., Klumpp, T. G., and Zschiesche, L. J., 143

- Weinstein, Israel, and Styron, N. C., 102,*
553*
- Weiss, Soma, and Davis, D., 45
and Ellis, L. B., 139*
and Robb, G. P., 742
- White, Paul D., and McGinn, S., 1, 642.
697
and Craig, H. R., 826*
- Wiggers, C. J., and Cotton, F. S., 272*
and Gregg, D. E., 545*
- Wile, S. A., and Saphir, O., 29
- Wilkins, Walter E., and Cullen, G. E.,
274*
- Wilson, Frank N., Hill, I. G. W., and
Johnston, F. D., 596
Johnston, F. D., and Barker, P. S., 472
Macleod, A. G., and Barker, P. S.,
447
Hill, I. G. W., Macleod, A. G., and
Barker, P. S., 459
- Winternitz, Max, 616
- Wolferth, Charles C., and Edelken, J.,
828*
and Wood, F. C., 127,* 706
Bellet, S., and McMillan, T. M., 276*
- Wolff, Louis, 133*
- Wood, Francis Clark, and Wolferth, C.
C., 127,* 706
Bellet, S., McMillan, T. M., and Wol-
ferth, C. C., 276*
- Wood, J. Edwin, Jr., and Gentile, R. J.,
530
Hart, A. D., and Daughton, A. D., 690*
- Woodall, Martin, Solomon, P., Hurwitz,
D., and Lamb, M. E., 134*
- Wright, Irving Sherwood, and Duryee, A.
W., 273*

Z

- Zschlesche, Louise J., Wearn, J. T., Met-
tier, S. R., and Klumpp, T. G.,
143

